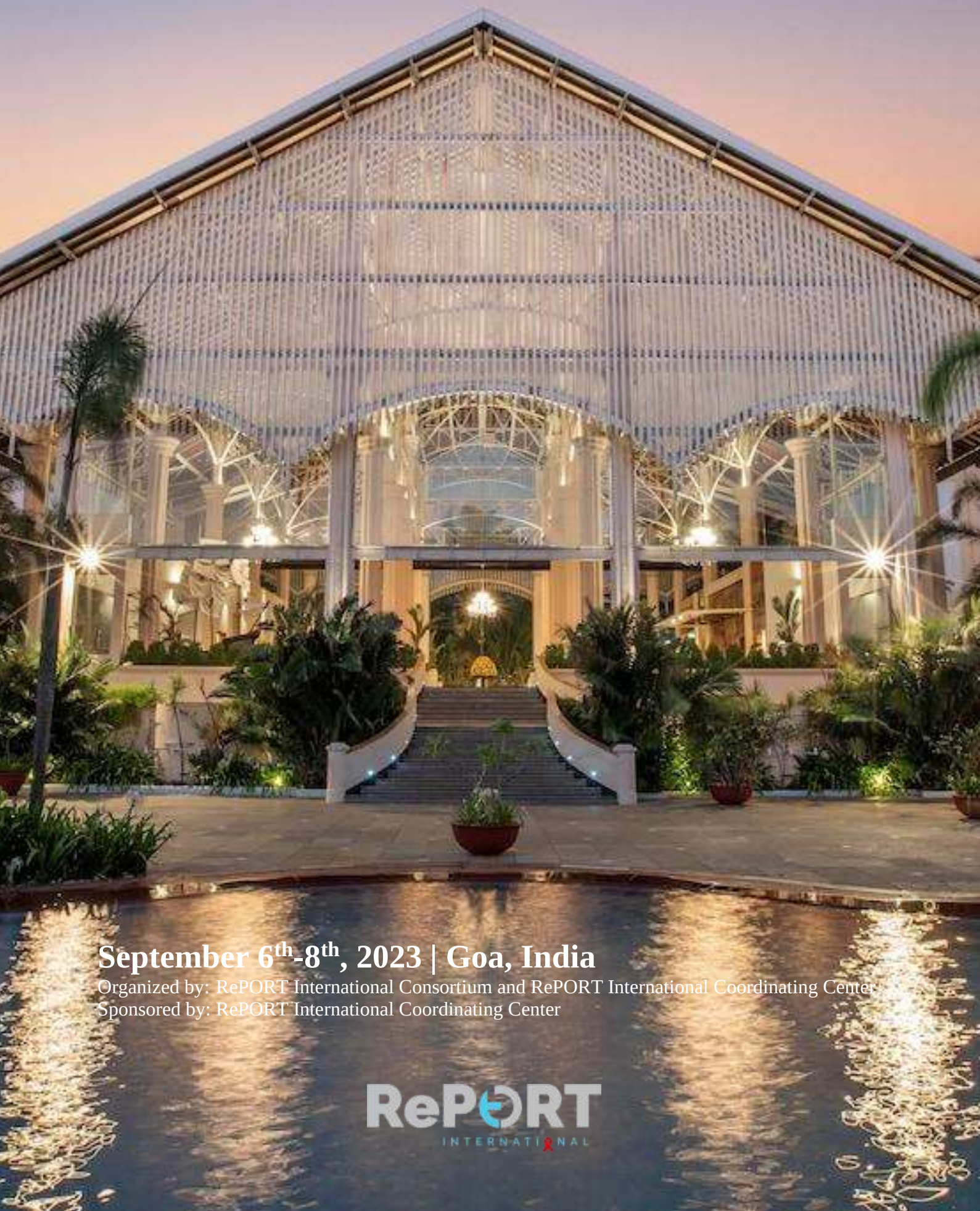
Regional Prospective Observational Research in Tuberculosis (RePORT)
7th Annual RePORT International Meeting



September 6th-8th, 2023 | Goa, India

Organized by: RePORT International Consortium and RePORT International Coordinating Center
Sponsored by: RePORT International Coordinating Center

Organized and Sponsored by: TB RePORT International Consortium and TB RePORT International Coordinating Center (TB-RICC)

National Institutes of Health, USA

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Welcome

We are delighted that you are here today to share and discuss the latest advancements and research in the field of tuberculosis with a focus on Early Tuberculosis. This meeting marks a "coming of age" for RePORT International. With a reformulated and enhanced Coordinating Center (RiCC 3.0), RePORT International is poised to achieve the vision as a platform for scientific discovery that will advance TB Science. Our focus is the discovery and generalizability of new tools for TB Control across populations. In that regard, this annual conference serves as a significant milestone in our shared journey.

The conference is organized to facilitate thought-provoking discussions, exchange cutting-edge research findings, and foster collaborations that transcend borders and boundaries. The success of this meeting and of RePORT International requires your participation, commitment, and dedication to our shared goals.

I would like to thank the Organizing Committee chaired by Drs. Sonali Sarkar and Camilla Rodrigues for forming an outstanding scientific program and acknowledge the roles of Ms. Daphne Martin and Ms. Joanna Radman for dealing with the complicated logistics that brought us to Goa. Thanks as well to NIH program (Drs. Sudha Srinivasan, Fatima Jones, and Peter Kim) for your tangible and intangible support.

The vibrant atmosphere of Goa offers the perfect backdrop to promote networking and camaraderie among fellow researchers, healthcare professionals, policymakers, and other stakeholders. We encourage you to take advantage of this opportunity to not only share your knowledge and expertise but also to learn from the experiences of others in the field.

Once again, welcome to the RePORT International Annual Meeting in Goa, India, with the hope that our time together be stimulating and impactful.

Jerrold J. Ellner MD

For the Organizing Committee and Leadership Group of RePORT International

Regional Prospective Observational Research in Tuberculosis
TB RiCC - RePORT International Annual Meeting
Meeting Agenda
September 6-8, 2023
Venue: LISBOA BALL ROOM, Radisson Blu Resort Goa Cavelossim

DAY 1 **RePORT International Meeting** **September 6, 2023**		
8:00-8:20 am	Registration (Outside LISBOA BALL ROOM)	
8:20-8:35 am	Welcome and Introduction	Sudha Srinivasan, National Institutes of Health, USA, Jyoti Logani, Department of Biotechnology, India & Jerry Ellner, RePORT International
8:35-8:50 am	Overview of RePORT India & RePORT International	Sonali Sarkar, RePORT India & Jerry Ellner, RePORT International
8:50-9:00 am	Role of RePORT International in NIAID TB Programs	Peter Kim/Fatima Jones, National Institutes of Health, USA
9:00-9:30 am	Keynote Address	
SESSION I	**Basic Research - MTb Survival**	
Facilitators:	**Dhiraj Kumar & Padmini Salgame**	
9:30-9:55 am	Delineating Survival Strategies Employed by Mycobacterium tuberculosis	Vinay Nandicoori, CSIR-Centre for Cellular and Molecular Biology
9:55-10:20 am	Targeting Host-Pathogen Heterogenous Interactions to Counteract Drug Tolerance in M. tuberculosis	Amit Singh, Indian Institute of Science (IISc) Bangalore
10:20-10:45am	Mycobacterium tuberculosis Biofilms: Their role in Drug Tolerance and Immune Evasion?	Ashwani Kumar, CSIR - Institute of Microbial Technology
10:45-11:00 am	**Coffee and Tea Break**	
SESSION II	**Vaccines**	
Facilitators:	**Amit Singh & Mark Hatherill**	
11:00-11:25 am	Vaccines to prevent TB Infection & Immunology	Mark Hatherill & Tom Scriba, RePORT South Africa
11:25-11:50 am	Vaccines: VPM	Umesh Shaligram, Serum Institute
11:50-12:15 pm	VPM1002 Overview and Immunology	Vidya Mave & Padmini Salgame, RePORT India

12:15-12:40 pm	VPM1002 ICMR Trial in Close Contacts	Manjula Singh, ICMR
12:40-1:00 pm	IeDEA Tuberculosis Sentinel Research Network (TB-SRN)	Jeremy Ross, IeDEA
1:00 – 1:20 pm	Innovation in AI Based TB Case Finding	Shibu Vijayan, Qure.ai
1:20 pm	**GROUP PHOTO (venue will be announced) & Lunch**	
Operational Agenda (Break Out Session – Members Only)		
2:30-4:00 pm	Bylaws Committee	Stephany Duda
4:00-4:15 pm	Tea break	LISBOA PRE FUNCTION AREA
4:15-5:45 pm	Scientific Review Committee	Tim Sterling & Mark Hatherill
6:30 pm	**Networking Dinner**	
DAY 2 RePORT International Meeting September 7, 2023 | 8:00 am		
8:00-8:15 am	Introduction and Overview of TB Survivors Program in India	Amita Gupta, RePORT India & Chapal Mehra, TB Survivors
8:15-8:30 am	A TB Survivor's Journey	Dipti Chavan, TB Survivors Program
8:30-8:50 am	Lung Health Study Updates	Hardy Kornfeld, UMass Chan Medical School - Worcester
Session III Early TB Facilitators: Vijaya Valluri & Bruno Andrade		
8:50-9:15 am	Subclinical TB - Community Study	Emily Wong, AHRI
9:15-9:40 am	PET-CT and Biomarkers in Subclinical TB	Anna Coussens, Walter and Eliza Hall Institute (WEHI)
9:40-10:05 am	Modeling Sub Clinical TB	Tess Rykman, Johns Hopkins University
10:05-10:20 am	Incidence and Determinants of Subclinical and Clinical Recurrence of Tuberculosis among Cured Pulmonary Tuberculosis Patients in India	Mandar Paradkar, RePORT India (Junior Investigator)
10:20-10:35 am	A comprehensive Multiomic analysis of the Tuberculosis and Diabetes Interaction	Mariana Araújo Pereira, RePORT Brazil (Junior Investigator)
10:35-10:50 am	**Coffee & Tea Break**	

Session IV Sub Clinical TB **Facilitators: DJ Christopher & Tim Sterling**		
10:50-11:05 am	Gene Signatures for Monitoring Treatment Response and Predicting Cure Among TB Patients in Brazil	Simon C Mendelsohn, RePORT South Africa (Junior Investigator)
11:05-11:20 am	Impact of Premorbid Nutritional Status on Tuberculosis Severity in India: a multicenter prospective cohort analysis	Komal Jain (on behalf of Xinyi Du), RePORT India (Junior Investigator)
11:20-11:35 am	The sound of silent RNA: The role of long non-coding RNA on Tuberculosis in four different populations	Artur Trancoso Lopo de Queiroz, RePORT Brazil (Junior Investigator)
11:35-11:50 am	Population Pharmacokinetics of Moxifloxacin in Indian Patients with Multidrug-Resistance Tuberculosis	Prerna Arora, RePORT India (Junior Investigator)
11:50-12:15 pm	IGRA Conversion/Reversion	Sheetal Verma, Rutgers University
12:15-12:40 pm	Immune Biomarkers for TB Progression in a Cohort Study of Household Contact	Prudhula Kamakshi, Bhagwan Mahavir Medical Research Centre
12:40-1:05 pm	Urine and Serum Biomarker Analyses in Cohort B samples from RePORT South Africa	Karen Dobos & John Belisle, Colorado State University
1:05-1:25 pm	Towards a Systems Pharmacology Mathematical Model for EPTB	Chetan Gadgil, National Chemical Laboratory, Pune
1:25-1:40 pm	Introduction to SMART4TB	Bob Bollinger, Johns Hopkins University
1:40 – 2:00 pm	Closing of Scientific Sessions	DJ Christopher & Mark Hatherill
2 pm	**POSTER SESSION & LUNCH BREAK**	
Operational Agenda (Break Out Session – Members Only)		
2:45 - 4:15 pm	Common Protocol	Stephany Duda & Ann Tufariello
4:15 - 4:30 pm	Tea Break	LISBOA PRE FUNCTION AREA
4:30 - 6:00 pm	Capacity Strengthening	Bob Bollinger & Valeria Rolla
Free Evening :)		

DAY 3 RePORT International Meeting September 8, 2023| 8:00 am		
Facilitators: Stephany Duda & Marissa Alejandria		
Scientific Country Updates		
8:00-8:20 am	RePORT Brazil	Country Representative
8:20-8:40 am	RePORT India	Country Representative
8:40-9:00 am	RePORT Indonesia	Country Representative
9:00-9:15 am	RePORT Korea	Country Representative
9:15-9:35 am	RePORT Philippines	Country Representative
9:35-9:55 am	RePORT South Africa	Country Representative
9:55-10:10am	RePORT Uganda	Country Representative
10:10-10:30 am	**Coffee & Tea Break**	
	Working Group & Protocol – Action Items & Approvals	
10:35-10:55 am	Biomarker Protocol	Padmini Salgame
10:55-11:15 am	Data Harmonization	Stephany Duda & Sri Ram Pentakota
11:15-11:35 am	Scientific Review Committee	Tim Sterling & Mark Hatherill
11:35-12:00 pm	Capacity Strengthening	Bob Bollinger
12:00-12:30 pm	Bylaws Committee	Stephany Duda
12:30-1:00 pm	Common Protocol	Stephany Duda & Ann Tufariello
1:00 pm	Closing & Lunch	Meeting Co-Chairs

Research Consortia and Partners

RePORT Overview

Tuberculosis (TB) remains one of the most significant infectious causes of mortality and morbidity worldwide and is the number one cause of death among those infected with the Human Immunodeficiency Virus (HIV). Major research needs to span from basic research to identifying biomarkers that accurately predict outcomes of active and latent TB, to clinical research to measure efficacy and effectiveness of new tools and strategies for TB. To meet this need, the ***US National Institute of Allergy and Infectious Diseases (NIAID)*** has created the Regional Prospective Observational Research in Tuberculosis (RePORT) International program to support the establishment of regional RePORT consortia in cooperation with host countries. This platform sets the stage for future combined or comparative data analyses and serves as an invaluable resource for in-country and cross-national collaborations between bench and clinical researchers.

Progress in TB clinical research is hampered by a lack of reliable biomarkers that predict progression from latent to active tuberculosis, and subsequent cure, relapse, or failure. RePORT International represents a consortium of regional cohorts (RePORT India, RePORT Brazil, RePORT South Africa, RePORT Indonesia, RePORT Philippines, RePORT China, RePORT Korea, and RePORT Uganda) that are linked through the implementation of a common protocol for data and specimen collection and are poised to address this critical research need. Each RePORT network is designed to support local, in-country TB-specific data and specimen biorepositories and associated research. Taken together, the expected results include greater global clinical research capacity in high-burden settings, and increased local access to quality data and specimens for members of each network and their domestic and international collaborators.

RePORT International Investigators, RePORT South Africa Host Team, NIH, and other Tuberculosis Scientists, attending the 6th Annual RePORT International Meeting, held in Cape Town, South Africa, September 2022.

RePORT Brazil

The Regional Prospective Observational Research in Tuberculosis (RePORT) Brazil network was established in August 2013 with funding from the Departamento de Ciência e Tecnologia (DECIT) – Secretaria de Ciência e Tecnologia (SCTIE) of the Ministry of Health of Brazil, and the National Institutes of Health of the United States. RePORT Brazil is a joint venture among the Departamento de Ciência e Tecnologia/Ministério da Saude (DECIT), the U.S. Office of AIDS Research and NIAID, co-funding a team of Brazil- and U.S.-based investigators to enroll people with active and latent TB in Brazil. Three sites in Rio de Janeiro, one in Manaus, and one in Salvador were selected to enroll TB cases and their close contacts (RePORT-Brazil Phase 1). During Phase 2 of enrollment (from 2022 to 2027), our plan is to enroll 1,000 new TB cases and 2,000 close contacts. The consortium sites represent a diverse population and enroll into a single protocol, which is harmonized with the RePORT International Common Protocol. Vanderbilt University Medical Center is the U.S.-based academic partner working with RePORT Brazil.

RePORT Brazil is led by a scientific and steering committee composed of researchers and members of NIH and Brazilian Ministry of Health, who provide leadership, governance, and guidance to the consortium. The current principal and co-investigators of RePORT Brazil are:

- Bruno Andrade, MD PhD, Salvador (RePORT PI and Biorepository Director)
- Valeria Rolla, MD PhD, Rio de Janeiro (Co-Investigator)
- Afrânio Kritski, MD PhD, Rio de Janeiro (Co-Investigator)
- Marcelo Santos, MD PhD, Manaus (Co-Investigator)
- Cristina Lourenço, Pharm., Rio de Janeiro (Microbiology Lab Director)
- José Roberto Lapa e Silva, MD PhD, Rio de Janeiro (Consultant)
- Anete Trajman, MD PhD, Rio de Janeiro (Consultant)
- Timothy Sterling, MD, Nashville (RePORT PI)

Phase 1:

Regional Prospective Observational Research in TB (RePORT)-Brazil began in 2013 and enrolled 1,188 pulmonary TB patients and 1,930 of their close contacts in Phase 1. Participants were followed for 24 months (through June 30, 2021), with *M. tuberculosis* (Mtb) isolates, sputum, blood, urine, DNA, RNA, and peripheral blood mononuclear cells (PBMCs) collected at baseline and during follow-up. Areas of scientific focus which received additional dedicated grant funding and led to several publications include: predictors of TB and TB/HIV treatment outcomes, predictors of Mtb infection and progression to TB disease and incipient TB, TB-diabetes, drug-resistant TB, and Mtb transmission. Collaborations have been established between investigators in Brazil and the United States, other RePORT networks (e.g., South Africa and India), the Caribbean Central America South America network for HIV epidemiology (CCASAnet) and its TB Sentinel Research Network (TB-SRN), part of the International epidemiologic Databases to Evaluate AIDS (IeDEA) network.

Phase 2:

Phase 2 of RePORT-Brazil will utilize the rich, high-quality clinical, genomic, and transcriptomic data generated in Phase 1, along with new participant enrollment, to extend our understanding of TB epidemiology and pathogenesis, and improve the diagnosis, treatment, and prevention of TB. This new phase will double the sample size of the cohorts, and the rare endpoints (such as TB in close contacts and recurrent TB in TB cases) that are needed to address key research questions in critical areas. We also expanded the enrollment criteria in Cohort A to include persons with TB symptoms (rather than just culture-confirmed pulmonary TB as in Phase 1), and thus allow evaluation of TB diagnostic tests. We expect to enroll:

- 1,000 microbiologically confirmed TB cases, including pulmonary (PTB), extrapulmonary (EPTB), of whom at least 20% are HIV+. Pregnant women and children will also be enrolled.
- 1,000 TB suspects who do not have microbiologically confirmed TB: either microbiologically-negative TB (i.e., clinical TB), or an alternative diagnosis.
- 2,000 close contacts of 1,000 microbiologically confirmed TB cases. Up to 4,000 contacts will be enrolled, but it is expected that up to 50% will be contacts of persons subsequently found to not have TB.

This will double the existing sample size from Phase 1 in Cohorts A and B and create a Cohort C of participants who do not have TB. Broadening the Cohort A enrollment criteria will allow us to expand beyond the focus in Phase 1 of culture-confirmed PTB in adults. The inclusion of persons suspected of having TB (not all of whom have TB) will allow us to better evaluate TB diagnostic tests. The inclusion of persons with EPTB, as well as pregnant women and children, will allow us to evaluate these important populations. Persons with HIV or diabetes mellitus will be included, as in Phase 1. This approach will enable us to assess the immune profile of individuals affected by TB and compare it with that of non-infected participants. Enrollment started in May 2022.

Objectives:

The primary objective of RePORT Brazil is to describe the clinical outcomes of TB treatment in Brazil, and the occurrence of *M. tuberculosis* infection and TB disease among close contacts of those TB source cases. To achieve this goal, RePORT Brazil focuses on:

1. Creating and maintaining a biorepository of clinical specimens and a database of well-characterized clinical endpoints for the TB cases and their close contacts.
2. Developing a scientific agenda that utilizes this specimen and data repository to improve our understanding of TB pathogenesis.
3. Establishing a TB laboratory and expanding clinical research infrastructure in Brazil.

Research Consortia:

RePORT-BR (TB-SRN-CCASAnet-IeDEA) – NIH

Background: The NIH-funded Caribbean, Central, and South America network for HIV epidemiology (CCASAnet) is the principal HIV epidemiology research network in Latin America and has an established 18-year track record of producing meaningful work.
Aims: To identify and quantify the systemic and individual determinants of outcomes among PWH in Latin America using comprehensive retrospective data and novel data science methodologies to inform clinical practices and health policy in the region. To characterize the contributions and consequences of psychosocial, behavioral, and non-communicable disease clinical outcomes in older adults, adolescents, and transgender persons with HIV through four nested prospective cohorts with enhanced data. To establish a new collaborative platform and common data framework for global tuberculosis epidemiology in persons with and without HIV for public health, clinical, and translational science discovery. This project also provides support for Cohort A infrastructure, including personnel, data management and quality. All RePORT-Brazil sites are involved.
Current status: Protocol approved at all Brazil sites and Phase 2 enrollment started in May 2022.
PI: Timothy Sterling, M.D., Valeria Rolla, M.D., Ph.D., Bruno Bezerril Andrade, M.D., Ph.D.

REPORT-BRAZIL PHASE 2 AND FELLOWSHIP IN TB SCIENCE

Background: Brazil has the highest tuberculosis (TB) burden in the Western Hemisphere, and among the highest in the world. Advances in TB diagnosis, treatment, and prevention are necessary to improve the incidence, morbidity, and mortality of TB in Brazil, and globally. RePORT-Brazil Phase 1 enrolled 1,188 TB cases and 1,930 close-contacts. The plan for phase 2 is to double the size of these cohorts.
Aims: Enroll an additional 1,000 TB cases and 2,000 close-contacts; Gain insights that improve TB diagnosis, treatment, and outcomes; improve our understanding of TB transmission and infection, predictors of progression to TB, and protection against TB; support and develop the next generation of TB scientists, and enhance the scope and collaboration of RePORT-Brazil.
Current status: Participants are currently being recruited at all RePORT-Brazil sites; Fellowship Program was launched in March 2023.
PI: Timothy Sterling, M.D., Bruno Andrade, M.D., Ph.D.

MAPPING *M. TUBERCULOSIS* TRANSMISSION HOTSPOTS USING PATIENT LOCATION HISTORY

Background: Mapping hotspots for transmission of infectious diseases can offer great help in controlling outbreaks and eliminating reservoirs of infection. Usually, hospital staff in endemic areas try to determine such places by asking patients with transmissible infections, those places where they live/work (for diseases which require chronic exposure) or visited a few days prior going to the hospital (for acute diseases). However, information obtained through questionnaires are generally vague, inaccurate and not integrated into databases. This makes the process manual, slow, and of little value for large-scale epidemiologic studies. Since a significant portion of the population has mobile phones with GPS, the objective of this project is to improve the accuracy and organization of *M. tuberculosis* infection networks, and to study the temporal dynamics of geolocalization data collected from TB patients. We are developing an online tool in which patients who arrive at referral centers can voluntarily provide GPS data of their mobile phones. User data will be anonymized, processed and sent to a secure server. By analyzing the location patterns of hundreds of patients during several months prior the clinical visit, we will be able to potentially map hotspots of *M. tuberculosis* transmission.

Aims: To use location history data from TB patients and their close contacts to find regions with a high risk of disease transmission. And to develop a web application to collect location history data from those patients diagnosed with TB and their close contacts, and implement a data analysis pipeline for finding the disease hotspots.
Current status: Participants are currently being recruited at all RePORT-Brazil sites.
PI: Helder Nakaya, Ph.D., Bruno Andrade, M.D., Ph.D.

TB/HIV: PREDICTORS OF TREATMENT TOXICITY, FAILURE, AND RELAPSE IN HIV RELATED TB – NIH

Background: This study is evaluating pharmacogenomic predictors of TB/HIV treatment toxicity, and TB treatment outcomes (e.g., 2-month culture conversion and failure/relapse). All RePORT-Brazil study sites enrolled participants into this study and several manuscripts are in preparation.
Aims: To identify pharmacogenomic predictors of TB/HIV plasma drug exposure and increased risk for toxicity during TB therapy; and to determine the pharmacogenomic predictors of two-month culture-positivity, and TB treatment failure and relapse, while accounting for host and *M. tuberculosis* pathogen factors.
Current status: All participants have been enrolled through RePORT-Brazil. An MTA was established so that the Biorepository in Brazil could ship the DNA and plasma samples to Vanderbilt (for genotyping and PK work, in which the assay to measure several TB and HIV drugs was developed). The ancestry informative markers (AIMs) evaluation was done in Brazil (Dr. Santos' lab). Several papers have been published and more are in preparation.
PI: Timothy Sterling, M.D., Valeria Rolla, M.D., Ph.D, David Haas, M.D.

PREDICTORS OF MECHANISMS OF EMERGENCE OF DRUG RESISTANCE IN MDR-TB (PREEMPT) – NIH

Background: This study will evaluate predictors of the emergence of resistance to drugs such as the fluoroquinolones among persons treated for MDR-TB. This study enrolled participants from INI (FIOCRUZ), Helio Fraga and the Federal University site in Rio de Janeiro.
Aims: Determine whether low serum antimycobacterial drug concentrations are associated with the clinical emergence of drug resistance in MDR-TB patients; Determine whether HIV seropositivity is a risk factor for low serum drug concentrations; Determine the contribution of increased DNA mutation to clinical emergence of drug resistance in patient isolates; and to determine the earliest time at which mutations responsible for drug resistance can be detected during treatment.
Current status: Participant follow-up continues. Analysis of pharmacokinetic (PK) and *M. tuberculosis* drug resistance data is underway.
PI: Robert Horsburgh, M.D., Timothy Sterling, M.D., Valeria Rolla, M.D., Ph.D., Afranio Kritski, M.D., Ph.D., Cristina Lourenço, Pharm.

IMMUNOGENETIC RISK FACTORS FOR INCIPIENT & ACTIVE TUBERCULOSIS – NIH

Background: The mechanisms and contribution of host genetic, immunologic, and epidemiologic factors to protection and predisposition to TB are poorly understood. To address that, we are using data and specimens collected in RePORT-Brazil, from ~2,000 close contacts of TB cases (Phase 1). After 2 years of follow-up of all close contacts, we identified those who progressed to TB disease and those at risk for incipient TB. This prospective study design will enable us to examine our primary hypothesis that there are immunogenetic pathophysiologic underpinnings of progressing to active TB (1°endpoint) and incipient TB (2° endpoint), and these variables, together with epidemiologic factors such as HIV, will improve predicting

progression to TB disease.
Aims: To determine which macrophage genes and variants are associated with protection against and risk of TB disease and incipient TB, and regulate anti-microbial mechanisms; to identify the *M. tuberculosis* antigen-specific T-cell responses associated with protection against and risk of TB disease and incipient TB; and to develop predictive models that determine the relative contribution of genetic, immunologic, transcriptomic, and epidemiologic factors for protection against and risk of TB disease and incipient TB in a cohort of close contacts of culture-confirmed TB in Brazil.
Current status: An award was received mid-June 2019. The protocol was approved at all IRBs at Vanderbilt University Medical center, RePORT-Brazil sites, the University of Washington, and the University of Cape Town. Enrollment is complete and lab assays, as well as analyses, are ongoing.
PI: Timothy Sterling, M.D., Thomas Hawn, Ph.D., Bruno Andrade, M.D., Ph.D., Thomas Scriba, Ph.D.

CHARACTERIZATION OF GENOMICS AND METABOLOMICS AMONG INDIVIDUALS HIGHLY-EXPOSED, BUT RESISTANT TO MTB INFECTION – NIH

Background: We will carefully measure exposure among household and close contacts to identify a cohort of persons who remain uninfected despite a high degree of exposure. We will then characterize genetic and metabolic factors associated with resistance. These data will inform our understanding of host factors that confer resistance, which will, in turn, inform the development of preventive therapeutics such as a TB vaccine.
Aims: To characterize a phenotype for resistance to Mtb infection using TST and IGRA results among household and close contacts recently exposed to TB; To determine genetic predictors for resistance to Mtb infection; and to identify metabolomic markers associated with resistance to Mtb infection.
Current status: RePORT-Brazil sites and Vanderbilt University Medical Center were added after the award was made. The protocol was approved by the local IRBs in Brazil and at Vanderbilt in May 2020. Approximately 2,000 close contacts were re-consented so data and specimens could be used for this study. DNA extraction has been finalized and genetic material sent to Emory for the TB-GWAS portion of the work. Analyses are underway. Plasma samples have been shipped for the metabolomics portion of the work.
PI: Neel Gandhi, Ph.D., Yan Sun, Ph.D , Timothy Sterling, M.D., Bruno Andrade, M.D, Ph.D, Marcelo Cordeiro Santos, M.D, Ph.D, Amita Gupta, Ph.D.

MACROPHAGE IMMUNOGENETICS AND INCIPIENT TUBERCULOSIS IN BRAZIL – CRDF GLOBAL

Background: The mechanisms and relative contribution of host genetic, immunologic, and epidemiologic factors to protection and predisposition to TB are poorly understood. Recent studies reported a host peripheral blood correlate of risk (COR) transcriptional signature that identified individuals at risk for incipient TB (asymptomatic) who progress to develop active (symptomatic) TB disease within 12 months in the absence of treatment. Signatures such as COR are transforming our understanding of the progression from Mtb infection to TB disease.
Aims: To utilize signatures such as COR to address current knowledge gaps in the immunogenetic basis of incipient TB and progression to disease.
Current status: An award was received in June 2019. The study protocol was submitted and approved at all IRBs in Brazil, UW and Vanderbilt. Participants were re-consented so that data and specimens could be used for this specific project. Lab assays and data analyses are ongoing.
PI: Thomas Hawn, Ph.D., Timothy Sterling, M.D., Bruno Andrade, M.D., Ph.D.

EVALUATION OF MICROVIRIN-BASED POINT-OF-CARE DIAGNOSTIC TESTS FOR TUBERCULOSIS

Background: Biomarker detection tests, such as enzyme-linked immunosorbent assays (ELISAs) and lateral flow assays (LFAs), are inexpensive and can be performed with minimal equipment. LFAs are particularly advantageous as they can provide results rapidly at the point-of-care (POC). The most commonly detected biomarker for TB is lipoarabinomannan (LAM). Currently, the only commercially-available LFA for LAM is the Alere LFA, which detects LAM in urine – a noninvasive, low biohazard risk sample method. However, due to low sensitivity, the Alere LFA is only approved for use in HIV-positive individuals as immunocompromised individuals have higher concentrations of LAM in urine. With increased sensitivity, an LFA could detect LAM in all individuals, regardless of immune status. Such an LFA would be an important advance in TB diagnostic tests, given its rapid turn-around-time and low-cost. Microvirin (MVN) is a lectin with a high affinity for alpha-1,2-mannose linkages, which are present in the endcaps of M.tb LAM. Using bio-layer interferometry, we have studied the binding of MVN to LAM and found the interaction to be of equivalent strength or stronger than the binding of LAM to anti-LAM antibodies. Furthermore, MVN has enhanced specificity for *M. tb*. Anti-LAM antibodies bind to the LAM backbone, which is common to LAM from all species of mycobacteria. In contrast, MVN binds to the endcaps of LAM, which vary according to the species of Mycobacterium. Thus, using MVN as a molecular recognition element to detect LAM in an LFA for diagnosis of TB would potentially result in a more sensitive and specific test compared to traditional LAM biomarker detection tests that utilize antibodies, while maintaining the speed and low cost that make LFAs so promising.

Aim: The purpose of this study is to evaluate the clinical performance of two diagnostic tests for TB: an on-bead ELISA and a lateral flow assay. Both tests use MVN to capture and detect LAM, a biomarker for TB, in urine.

Current status: The study protocol has been approved by the IRBs in Brazil and participants were re-consented, so that data and specimens could be used for this specific project. Lab assays are ongoing, led by Dr. Adriano Gomes in Brazil.

PI: David Wright, Ph.D., Megan van der Horst, Micaella Jorge, Valeria Rolla, M.D., Ph.D, Adriano Gomes, Ph.D, Timothy Sterling, M.D.

INNOVATIVE MODELLING FOR PREDICTING TB TREATMENT OUTCOMES IN GLOBAL COHORTS – CRDF GLOBAL

Background: A subset of tuberculosis patients experience treatment failure, recurrence, or progress to death, either during treatment or in the months following its completion. Despite numerous studies describing clinical and laboratory risk factors associated with unfavorable outcomes, few have generated and validated clinically useful prognostic models.

Aims: Our main aim is to develop and validate parsimonious models of baseline and longitudinal clinical data using traditional statistical methods, LASSO, and machine learning techniques. Using this methodology, we will assess the impact of co-conditions such as diabetes, alcohol use, HIV and malnutrition on adverse TB treatment outcomes. Our second aim will assess the additional contribution of molecular biomarkers such as inflammatory cytokines and gene signatures in predicting adverse outcomes, allowing us to identify critical biomarkers and remove low-performing markers.

Current status: This study will be part of RePORT-Brazil Phase II and protocol amendments were submitted and approved at all IRBs in Brazil, India and in the U.S.

PI: Bruno Andrade, M.D., Ph.D., Timothy Sterling, M.D., Matthew Robinson, M.D., Nikhil Gupte, Ph.D., Gustavo Amorim, Ph.D., Moreno Rodrigues, Ph.D., Sonya Krishnan, MD.

ASSOCIATIVE BRICS RESEARCH IN COVID-19 AND TUBERCULOSIS (ABRICOT) – CRDF GLOBAL & CNPQ

Background: The COVID-19 pandemic has provided new challenges for TB control. However, there is limited information on the effect of severe COVID-19 on TB immunopathogenesis and how this affects, if at all, TB treatment outcomes.

Aims: To investigate: a) the impact of COVID-19 lymphopenia or hyperinflammation on specific- TB immune responses; b) the impact of COVID-19 on complement system activation and consequent hyperinflammation; and c) the correlation of these immune responses with TB outcomes.

Current status: The study protocol has been developed and was approved at the INI IRB in Brazil, as well as NIRT in India, and PHRU sites in South Africa. Enrollment is complete in Brazil.

PI: Valeria Rolla, M.D., Ph.D., Timothy Sterling, M.D., Bavesh Kana, Ph.D., Subash Babu, Ph.D.

EPIDEMIOLOGICAL FACTORS ASSOCIATED WITH TB TREATMENT OUTCOMES ACROSS REPORT INTERNATIONAL CONSORTIA – CRDF GLOBAL

Background: Several clinical factors have been associated with poor TB treatment outcomes. Key factors such as malnutrition, anemia, tobacco smoking, alcohol use, drug use, HIV infection, and previous TB infection may be independent predictors of poor TB treatment outcomes.

Aims: To determine the impact of key non-communicable and communicable diseases on tuberculosis treatment outcomes and recurrence using data from multiple RePORT International consortia.

Current status: Study protocol has been developed and was approved at all RePORT sites. Data are being merged and analysis is ongoing.

PI (Brazil):Valeria Rolla, M.D., Ph.D., Timothy Sterling, M.D., Bruno Andrade, Ph.D.

ANALYSIS OF HOST BIOMARKERS ASSOCIATED WITH ADVERSE TB TREATMENT OUTCOMES ACROSS REPORT INTERNATIONAL SITES – CRDF GLOBAL

Background: Diagnostic accuracy of biomarkers may be impacted by ethnicity and co-morbidities, therefore performance of these biomarkers should be evaluated across diverse populations.

Aims: The overall goal is 1) to expand the validation studies of host biomarkers associated with TB treatment failure proposed at each RePORT site; 2) to cross validate the biomarkers in samples across RePORT International Consortia; and 3) to identify a biomarker of "cure" using a discovery-based approach.

Current status: Study protocol has been developed and was approved at all RePORT sites. Material Transfer Agreements are being executed, so samples can be shipped across countries.

PI (Brazil): Timothy Sterling, M.D., Bruno Andrade, Ph.D.

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RePORT China

The RePORT China consortium is a collaborative network with the leadership and funding from China TB Clinical Trial Consortium (CTCTC), Innovation Alliance on TB Diagnosis and Treatment (Beijing) (IATB), and with technical support from NIH. The RePORT China consortium joined RePORT International in January 2017 after signing the RePORT International Memorandum of Understanding. RePORT China followed the bylaws, which set clear guidelines and expectations for current and future groups to work together on a broad set of common goals. China consortium developed a locally-tailored study protocol, manual of laboratory operations, and case report forms (CRFs) for qualified case enrollment, sample collection and storage, data collection and sharing based on the Common Protocol and biorepository standards by RePORT International. Currently, the target enrollment for RePORT China is 180 participants, with the actual number at 198. Samples originated from blood, urine and sputum were collected and stored with the total number at 12,480.

RePORT China works closely with the RePORT International consortium by participating in monthly call conferences with RePORT International members to discuss the RePORT work progress, data harmonization, and by actively participating in annual RePORT International meeting planning. The RePORT China consortium has cooperated and is seeking opportunities to cooperate with other RePORT consortia members to do cross-consortium research including utilizing data and specimens collected to explore TB biomarkers host immunity effect. Currently 7 sites remain active under RePORT China, including Beijing Chest Hospital, Changsha Central Hospital, The Third People's Hospital of Zhenjiang, Fuzhou Pulmonary Hospital, Tianjin Haihe Hospital, Suzhou Fifth People Hospital, and Jingzhou Chest Hospital.

China Project Descriptions and Principal Investigators:

RePORT China is funded locally by the Innovation Alliance on TB Diagnosis and Treatment (Beijing). The Principal Investigators (PIs) are Drs. Li-ang Li and Liu Yuhong and Dr. Gao Jingtao as Co-PI at country level.

Currently, the consortium consists of the following sites:

- Beijing Chest Hospital, Capital Medical University (Dr. Gao Mengqiu)
- Changsha Central Hospital (Dr. Li Chunxiang)
- The Third People's Hospital of Zhenjiang (Dr. Pan Hongqiu)
- Fuzhou Pulmonary Hospital (Dr. Chen Xiaohong)
- Tianjin Haihe Hospital (Dr. Mei Zaoxian)
- Suzhou NO.5 People's Hospital (Dr. Wu Meiying)
- Jingzhou Chest Hospital (Dr. Zhu Jinling)

Research Consortia:

DYNAMIC DETECTION OF CYTOKINES BY LIQUID CHIP TECHNOLOGY TO EVALUATE THE EFFICACY OF ANTI-TUBERCULOSIS TREATMENT

Aims: To find reliable indicator to achieve early and accurate evaluation of anti-tuberculosis efficacy.

PI: Dr. Huang Hairong, Josephine Aldaba.

PHARMACOKINETIC ASSESSMENT OF MDR-TB DRUGS IN THE TREATMENT OF TB MENINGITIS

Aims: To characterize the plasma and CSF drug levels of participants receiving second-line TB drugs in population PK models and explore the relationship between drug exposures plus isolate sensitivities and outcomes, namely vital status and functional status.

PI: Drs. Jeffrey A Tornheim, Camilla Rodrigues, Zarir F Udwadia, Duan Hongfei

RePORT India

RePORT India is a bilateral, multi- organizational, collaborative research effort established in 2013 under the Indo-US Vaccine Action Program (VAP). RePORT India is now the largest of eigh regional RePORT consortia (China, Brazil, Indonesia, Korea, Philippines, South Africa, and Uganda) that also participate in multi-organizational tuberculosis (TB) research efforts. Each RePORT consortium is designed to support local, in-country, TB-specific data and specimen biorepositories and associated research. Taken together, the anticipated results include greater global clinical research capacity in high-burden settings and increased local access to quality data and specimens for members of each consortium and their domestic and international collaborators. Leveraging the data, specimens, infrastructure, and scientific partnerships established by RePORT India in Phase I, the consortium has now launched Phase II.

Mission:

RePORT India is charged with:

1. Advancing regional TB science in India, towards fulfilling the TB strategic goals of the country
2. Strengthening TB research capacity and infrastructure
3. Fostering research collaboration within India and with other countries focused on research that can lead to clinically important biomarkers, vaccines, drugs, and diagnostics.

Phase I – Parent Protocols:

Phase I (2013–2018) commenced with six Clinical Research Sites (CRSs) in Western and Southern India that were partnered with five U.S. academic institutions. P.D. Hinduja National Hospital and Medical Research Centre was subsequently added as the seventh Indian site. Initially, each site had its own "Parent Protocol" with distinct research topics. Clinical, behavioral, radiological, and biological samples were collected from the enrollees, including sputum, blood, urine, etc. The specimens were stored at the ICMR-NIRT biobank for scientific analysis. TB patients and their household contacts were followed for a period of two years.

Cohort A:

Participants who have active TB disease. Studies involving this cohort of patients focused on TB diagnosis and treatment outcomes.

- 2455 patients enrolled with TB inside the lungs (including 133 with drug-resistant TB)
- 588 patients enrolled with TB outside the lungs
- 207 children enrolled with TB

Cohort B:

Participants who are household contacts (HHCs) of an active case of TB. Studies involving this cohort of participants focused on risk of infection and progression to TB disease after exposure.

- 3766 HHCs of coughing adult patients with TB inside the lungs enrolled.

Phase I – Parent Protocol Achievements:

- 106 scientific publications to advance TB science and public health.
- 64 new projects utilizing the collected and stored samples for new biomarkers.

- 245 presentations to showcase the work done in the RePORT Consortium.
- New child TB diagnosis and treatment response gene-signatures unique for India.
- New Transcriptomic, Lipidomic and Metabolomic signatures as blood biomarkers.
- New vaccine trials to prevent TB relapse.
- Clinical biomarkers of TB death and relapse. Key public health finding that informed the country's National TB Elimination Program guideline policies and more public health findings in the list with potential to guide further.

Phase I – Common Protocol:

Based on the tremendous productivity of RePORT India's Phase I in identifying new blood-based, sputum-based and urine-based biomarkers that can diagnose TB or predict TB patients' treatment success or failure or death, and for assessing new vaccines to prevent getting TB again (relapse) for those starting TB treatment, the governments of India and the US bilaterally funded the extension of Phase I into a "Common Protocol" in 2017. The Common Protocol allowed for standardized data elements and harmonized procedures for enrollment across all sites to 1) identify newer, more accurate biomarkers and 2) confirm the utility of previously discovered biomarkers by validating them on samples stored in the ICMR-NIRT sample bank. The Common Protocol enrolled and followed TB patients and their HHCs for a period of two years.

Cohort A: Participants who have active TB disease.

- 724 adult patients enrolled with TB inside the lungs

Cohort B: Participants who are household contacts (HHCs) of an active case of TB.

- 898 household contacts of coughing adult patients with TB inside the lungs enrolled.

BMMRC & UTT:

- Topic of Study: Immunologic Markers of Persons at Highest Risk of Progression of Latent TB Infection to TB
- India PI: Dr. Vijaya Valluri, Bhagawan Mahavir Medical Research Centre (BMMRC), Hyderabad, India
- U.S. PI: Dr. Krishna Vankayalapati, University of Texas Health Science Center, Tyler (UTHCT), TX, USA
- Participating Patient Cohort: Cohort B

BMMRC

BJGMC, NIRT, & JHU:

BJGMC

- Topic of Study: Host and Microbial Factors Associated with Poor Treatment Response and Progression to Active TB (C-TRIUMPH)
- India PIs: Drs. Sanjay Gaikwad, Aarti Kinikar and Shashikala Sangle, Byramjee Jeejeebhoy Government Medical College (BJGMC), Pune, India; Dr. Vidya Mave, BJGMC-JHU CRS, Pune, India; Drs. Padma Chandrasekaran and Bhavani PK, National Institute for Research in TB (NIRT), Chennai, India
- U.S. PI: Dr. Amita Gupta, Johns Hopkins University, Baltimore, MD, USA
- Participating Patient Cohorts: Cohort A (Adult Pulmonary TB, Pediatric TB, and Extrapulmonary TB) and Cohort B

CMC Vellore & U of Wash/U of Cambridge:

CMC-Vellore

- Topic of Study: Host Determinants in the Eicosanoid Pathway that Modulate the Inflammatory Response, Disease Outcome, and Treatment Responsiveness in TB
- India PI: Drs. DJ Christopher and Balamugesh Thangakunam, Christian Medical College (CMC), Vellore, India
- U.S. PI: Dr. Lalitha Ramakrishnan, University of Washington, Seattle, WA, US/University of Cambridge, UK
- Participating Patient Cohort: Cohort A (Adult Pulmonary TB and TB Meningitis)

Hinduja & JHU:

- Topic of Study: MDR-TB Treatment Outcomes, Adverse Effects, Mtb Genotyping, and Pharmacokinetic Testing
- India PIs: Drs. Zarir F. Udwadia, Tester F. Ashavaid, and Camilla Rodrigues; P.D. Hinduja National Hospital and Medical Research Centre, Mumbai, India
- U.S. PIs: Drs. Amita Gupta and Jeffrey Tornheim, Johns Hopkins University (JHU), Baltimore, MD, USA
- Participating Patient Cohorts: Cohort A (Adult/Adolescent MDR-TB) and Cohort B

JIPMER, BU/BMC, & Rutgers:

- Topic of Study: Biomarkers for Risk of TB and for TB Treatment Failure and Relapse
- India PIs: Drs. Gautam Roy and Sonali Sarkar, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

- U.S. PIs: Drs. Jerry Ellner and Padmini Salgame, Rutgers University, Newark, NJ, USA; Dr. Robert Horsburgh, Boston University (BU), Boston, MA, USA; Dr. Natasha Hochberg, Boston Medical College (BMC), Boston, MA, USA
- Participating Patient Cohorts: Cohort A (Adult Pulmonary TB and Pediatric TB) and Cohort B

MVDRC, NIRT-ICER, UMass:

- Topic of Study: Effects of Diabetes and Prediabetes on TB Severity
- India PIs: Dr. Vijay Viswanathan, MV Diabetes Research Centre (MVDRC), Chennai, India; Dr. Subash Babu, National Institute for Research In Tuberculosis (NIRT) – International Centers for Excellence in Research (ICER), Chennai, India
- U.S. PI: Dr. Hardy Kornfeld, University of Massachusetts (UMass) Medical School, Boston, MA, USA
- Participating Patient Cohort: Cohort A (Adult Pulmonary TB)

Phase II – Common Protocol:

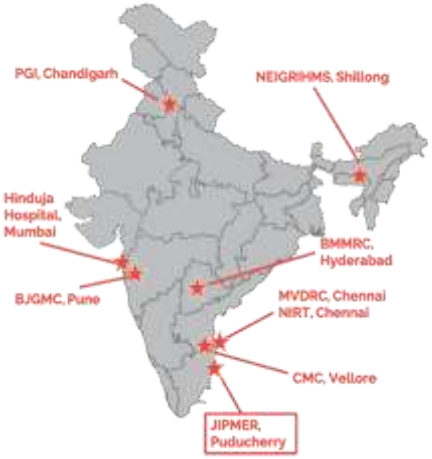
Both Indo-US governments have further supported the scientific research goals of RePORT India by expanding the number of sites represented across the country, especially by involving scientists and participants from the Northern and North-eastern parts of the country. In addition to the existing group of TB patients and their household contacts across nine Indian sites in the RePORT India Phase II Common Protocol, the consortium plans to support the enrollment of 1500 adult and child patients who are suspected of having TB inside or outside their lungs, 588 adult patients with TB inside the lungs, and 794 household contacts of adult patients with TB inside the lungs. On the following pages, the Phase II CRSs and their study focus areas are outlined.

Phase II – Common Protocol Expected Achievements

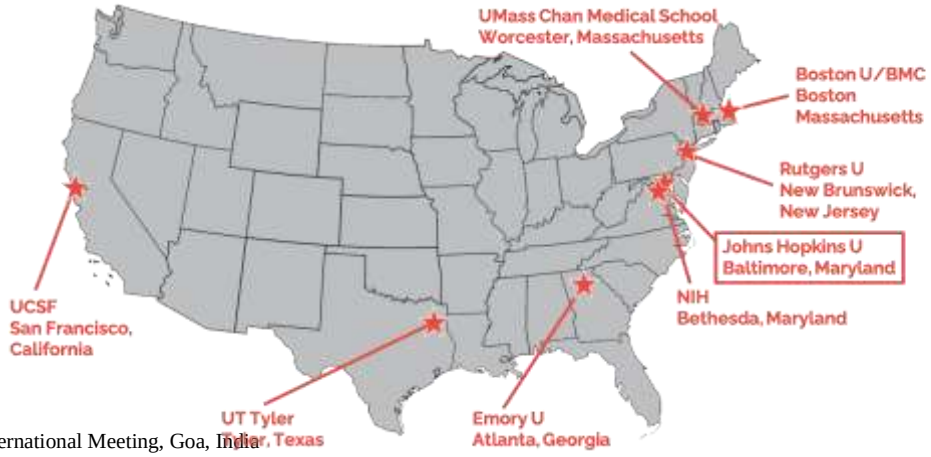
- Enhanced collaborative TB research with Indian and US Scientists spanning clinical epidemiology to translational science
- Tested and validated a number of novel diagnostics of diverse spectrum TB states
- Validated the parsimonious gene expression profiles for TB treatment monitoring (i.e., TB treatment failure vs. cure; treatment occurrence vs. cure)
- Validated the gene expression profiles for patients with comorbidities

- Examined PK of first line TB drugs for Indian patients on daily TB treatment who have under-nutrition and/or diabetes to guide treatment decisions
- Examined the sequalae of TB that results in persistent lung impairment despite microbiologic cure
- Identified mechanisms of resistance to Mtb infection
- Validated PREDICT29 biomarkers for progression to disease
- Discovered new biomarkers of progression to disease after exposure
- Examined the role of T4 hormone in TB disease progression
- Curated a well characterized biorepository available for new collaborations and funding

RePORT India Phase II



Under a Phase II Common Protocol, we are pursuing five specific scientific aims including the following cohorts: Diagnostic (New TB suspects), Cohort A (Active TB disease), and Cohort B (HHCs). Samples collected under this protocol will be curated, stored, and managed at the RePORT India Central Biorepository at NIRT where Phase I Common Protocol samples are currently stored. A data management center has been established at JIPMER in Puducherry and PPD will continue to provide technical support. The Phase II Common Protocol Co-Chairs are: Drs. Kamakshi Prudhula Devalraju (BMMRC) and Robert Bollinger (JHU). The consortium has been expanded to include two new CRSs in Northern India.



Phase II Scientific Aims

AIM 1. DIAGNOSTICS

Evaluate Novel Diagnostics & Biomarkers of Diverse States of Mtb Infection

Participating Patient Cohort: Diagnostic (New TB suspects)
Leads: Dr. Sonali Sarkar (JIPMER) and Dr. Jerry Ellner (Rutgers)
Participating Patient Cohort: Cohort B (XDR HHCs)
Leads: Dr. Tester Ashavaid (Hinduja) and Dr. Jeff Tornheim (JHU)

AIM 2. MARKERS OF TREATMENT RESPONSE

Participating Patient Cohort: Cohort A (Active TB disease)
2.A: Identify TB Treatment Response Biomarkers
Leads: Dr. Vijay Viswanathan (MVDRC) and Dr. Hardy Kornfeld (UMass)
2.B: Investigate Host-Related Mechanisms of Treatment Failure
Leads: Dr. Vidya Mave (BJGMC-JHU CRS) and Dr. Pranay Sinha (BMC)
2.C: Investigate Pathogen-related Mechanisms & Predictors of Recurrence
Lead: Dr. David Alland (Rutgers)

AIM 3. LUNG INJURY & IMPAIRMENT

Identify Markers of Lung Injury Associated with Unfavorable TB Treatment Outcomes

Participating Patient Cohort: Cohort A (Active TB disease)
Leads: Dr. DJ Christopher (CMC Vellore), Dr. Ashutosh Aggarwal (PGI Chandigarh), and Dr. Akshay Gupte (JHU)

AIM 4. RESISTANCE TO INFECTION

Mechanisms of Protection against TB in Exposed Persons

Participating Patient Cohort: Cohort B (Phase I HHCs)
4.A: Examine Host Antimicrobial Pathways in Inducing their infection resistant (IR) Phenotype in HHC
4.B: Test if IR & Plasma Differ in Modulating Macrophage-Mediated Restriction of Mtb Growth & Evaluate AB Repertoires of Plasma from the IR and infection susceptible (IS) Cohorts
Leads: Dr. Padmini Salgame (Rutgers), Dr. Subash Babu (NIRT-ICER), and Dr. Kamakshi Prudhula Devalraju (BMMRC)

AIM 5. PROGRESSION TO DISEASE

Identify Immunologic Markers of Persons at Highest Risk of Progress of Latent TB Infection to TB

5.A: Stored Samples: Validation of PREDICT29 in Progressors & Nonprogressors from RePORT Sites
Participating Patient Cohort: Cohort B (Phase I HHCs)
Leads: Dr. Padmini Salgame (Rutgers) and Dr. Luke Elizabeth Hanna (NIRT)
5.B: Immune & Hormone Studies in Freshly Collected Samples
Participating Patient Cohort: Cohort B (Phase II HHCs)
Leads: Dr. Vijaya Valluri (BMMRC) and Dr. Ramakrishna Vankayalapati (UTT)

In addition to these five aims, we will assess cross-cutting epidemiologic and COVID-19 related aims.

Grants

TITLE	PARTNERS	GRANT SOURCE	START DATE
Local Capacity Building to Develop Novel Drug-Resistant TB Testing and High-Throughput Multiplex Protein Measurement Programs in Pune, India	BJGMC	NIH	2023
RePORT India Consortium Strengthening Equipment Funding	Hinduja; BJGMC	NIH	2023
TB-RiCC Laboratory Enhancement and Capacity Building	Rutgers, JIPMER	RICC	2023
IFNg-independent T cell-mediated protection in Mycobacterium tuberculosis infection.	Rutgers, JIPMER	RICC	2022
Microbiome-Associated Effects of Diabetes and BMI on Tuberculosis Severity	MVDRC, UMass	NIH	Submitted 2020 - Pending
Learning Effect of Parasites and Reinforcing Diets on TB (TB-LEOPARD)	JIPMER, BU	Burroughs-Wellcome Fund	2022
Dynamics and Immune Mechanisms of QFT Response in Close Contacts of TB Cases	JIPMER, BU	NIH/NIAID Supplement	2022
Rapid Research for Diagnostics Development in TB Network	CMC Vellore, UCSF	NIH/NIAID R01	2021
Innate Immune Response of LTBI+HIV+ Children	BMMRC, UT	NIH/NIAID R01	2021
Impact of Latent TB Infection and Trained Immunity on Susceptibility to SARS-CoV- 2 Infection in India and the Philippines	Rutgers, JIPMER, University of the Philippines-Manila	RICC	2021
Learning about Experience with Nutritional Supplementation in Tuberculosis (LENS): An Exploratory Study	JIPMER, BU	Boston University of India (Seed Grant)	2021
Understanding Mycobacterium tuberculosis Mediated Host Metabolomics in Pulmonary Tuberculosis: Correlation with Disease Severity and Treatment Course	JIPMER IISER, Pune	PEER Women in Science SEED Grants 2021: National Academies	2021
The Regional Prospective Observational Research for Tuberculosis (RePORT) India Phase II Common Protocol	CMC Vellore	EC Approved	2020
Hybrid Trial for Alcohol Reduction among People with TB and HIV in India (HATHI)	BJGMC, JHU, London School of Hygiene and Medicine, DY Patil	NIH NIAAA R01	2020

TITLE	PARTNERS	GRANT SOURCE	START DATE
Signature of Profiling and Staging the Progression of TB from Infection to Disease		NIH R01	2020
VITAL TB (Vitamins And Latency in Tuberculosis)	JIPMER, BU	U.S. Dept of State's Partnership 2020 educational initiative	2020
Thyroxine (T4) Hormone Inhibits Expansion of Immunosuppressive CD4CD25+Foxp3+ (Tregs) Cells (Administrative Supplement for current R01 "IFN- independent inhibition of MTB growth in human macrophages")	BMMRC, UT	R01	2020
Host and Microbiome Transcriptional Profiling in the Upper Airways for TB Susceptibility	JIPMER	CTSI Pilot Grant, BU, US	2020

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1. Metabolites enhance innate resistance to human Mycobacterium tuberculosis infection. Tripathi D, Devalraju KP, Neela VSK, Paidipally P, Radhakrishnan RK, Mukherjee T, Dozmorov I, Bogam AK, Mallidi V, Ansari MS, Valluri VL, Vankayalapati R. JCI Insight. 2022 Nov 22;7(22):e152357. doi: 10.1172/jci.insight.152357. PMID: 36509283; PMCID: PMC9746823.

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1. Characterising cause of death among people treated for drug- susceptible TB in India Cox SR, Padmapriyadarsini C, Mave V, Seth B, Thiruvengadam K, Gaikwad S, Sahasrabudhe TR, Sane M, Tornheim JA, Shrinivasa BM, Lokhande R, Barthwal MS, Shivakumar VBY, Krishnan S, Santhappan R, Kinikar A, Kakrani AL, Paradkar M, Bollinger RC, Sekar K, Gupte AN, Hanna LE, Gupta A, Golub JE, on behalf of the CTRIUMPH and TBDM Study Teams. Int J Tuberc Lung Dis. 2023;27(1):78-80. http://dx.doi.org/10.5588/ijtld.22.0454
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3. QuantiFERON supernatant-based host biomarkers predicting progression to active tuberculosis disease among household contacts of tuberculosis patients. Daniel EA, Thiruvengadam K, Rajamanickam A, Chandrasekaran P, Pattabiraman S, Bhanu B, Sivaprakasam A, Paradkar M, Kulkarni

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5. Whole genome sequencing assessing impact of diabetes mellitus on tuberculosis mutations and type of recurrence in India. Mave V, Chen L., Ranganathan U D, Kadam D, Vishwanathan V, Lokhande R, S, S. K., Kagal, A, Neeta, Shivakumar SVBY, Paradkar MS, Deshmukh S, Tornheim JA, Kornfeld H, Farhat M, Gupta A, Padmapriyadarsini C, Gupte N, Golub JE, Mathema B, & Kreiswirth BN. Clin Infect Dis. 2022 Sep 14;75(5):768-776. doi: 10.1093/cid/ciab1067. PMID: 34984435; PMCID: PMC9477453.

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1. Accuracy of Xpert MTB/RIF Ultra for the diagnosis of tuberculosis in adult patients: a retrospective cohort study. Kaswala C, Schmiedel Y, Kundu D, George MM, Dayanand D, Devasagayam E, S AM, Kumar SS, Michael JS, Ninan MM, Chacko G, Zachariah A, Sathyendra S, Hansdak SG, Iyadurai R, Christopher DJ, Gupta R, Karthik R, Abraham OC, Varghese GM. Int J Infect Dis. 2022 Sep;122:566-568. doi: 10.1016/j.ijid.2022.07.016. Epub 2022 Jul 8. PMID: 35811084.

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Jawaharlal Institute of Postgraduate Medical Education & Research Boston Medical Center/Boston University/Rutgers (CRU 102)

1. Psychometric properties of the Household Food Insecurity Assess Scale among households with tuberculosis patients in South India. (Accepted in Progress in Nutrition) Yuvaraj Krishnamoorthy, Sathish Rajaa, Komala Ezhumalai, Selby Knudsen C, Robert Horsburgh Jr., Natasha S. Hochberg, Padmini Salgame, Jerrold Ellner, Senbagavalli PB, Sonali Sarkar

2. Comparison of IGRA and TST in the diagnosis of latent tuberculosis among women of reproductive age in South India. Senbagavalli Prakash Babu, Komala Ezhumalai, Kalaivani Raghupathy, Madhusudanan Sundaresan, Komal Jain, Prakash Babu Narasimhan, Selby Knudsen, Robert Horsburgh, Natasha Hochberg, Padmini Salgame, Jerrold Ellner, Sonali Sarkar. Indian Journal of Tuberculosis https://doi.org/10.1016/j.ijtb.2022.03.011.

3. Effect of treatment adherence on the association between sex and unfavourable treatment outcomes among tuberculosis patients in Puducherry, India: a mediation analysis. Barathi A, Krishnamoorthy Y, Sinha P, Horsburgh C, Hochberg N, Johnson E, Salgame P, Govindarajan S, Senbagavalli PB, Lakshinarayanan S, Roy G, Ellner J, Sarkar S. J Public Health (Oxf). 2022 Jun 11:fdac062. doi: 10.1093/pubmed/fdac062. Epub ahead of print. PMID: 35692180.

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7. Impact of Undernutrition on Tuberculosis Treatment Outcomes in India: A Multicenter Prospective Cohort Analysis. Sinha P, Ponnuraja C, Gupte N, Babu SP, Cox SR, Sarkar S, Mave V, Paradkar M, Cintron C, Govindarajan S, Kinikar A, Priya N, Gaikwad S, Thangakunam B, Devarajan A, Dhanasekaran M, Tornheim JA, Gupta A, Salgame P, Christopher DJ, Kornfeld H, Viswanathan V, Ellner JJ, Horsburgh CR, Gupte AN, Padmapriyadarsini C, Hochberg NS. Clin Infect Dis. 2022 Nov 25:ciac915. doi: 10.1093/cid/ciac915. Epub ahead of print. PMID: 36424864.

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MVDRC, NIRT-ICER, UMass

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2. Longitudinal Trends in Glycated Hemoglobin During and after Tuberculosis Treatment Kornfeld H, Procter-Gray E, Kumpatla S, Kane K, Li W, Magee MJ, Babu S, Viswanathan V. Diabetes Res Clin Pract. 2023 Jan 7:110242. doi: 10.1016/j.diabres.2023.110242. Online ahead of print.. PMID: 36627027

3. Heightened microbial translocation is a prognostic biomarker of recurrent tuberculosis Kumar NP, Moideen K, Viswanathan V, Sivakumar S, Ahamed SF, Ponnuraja C, Hissar S, Kornfeld H, Babu S. Clin Infect Dis. 2022 Nov 14;75(10):1820-1826. doi: 10.1093/cid/ciac236. PMID: 35352112; PMCID: PMC9662171.

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ADMINISTRATION:

RePORT India has established a collaborative governance structure composed of: 1) an Executive Committee led by two Chairs and two Co-chairs from India and the U.S.; 2) an Indo-U.S. Coordinating Hub; 3) three Scientific Working Groups (Basic Science, Clinical Epidemiology, Behavioral Science); 4) five Operational Working Groups (Common Protocol Leadership, Study Coordination, Publications Committee, Laboratory Management, and Data Management); and 5) a Data Coordinating Hub (JIPMER). The EC's mission is to set research priorities, guide scientific activities, and offer administration and logistics in support of research priorities.

The consortium is currently led by:

- Chairs: Dr. Sonali Sarkar (JIPMER, Clinical Epi) and Dr. Amita Gupta (JHU, Clinical Epi)
- Co-Chairs: Dr. Vijaya Valluri (BMMRC, Basic Science) and Dr. Padmini Salgame (Rutgers, Basic Science)

Funding:

The RePORT India Consortium is supported with bilateral funding from the Government of India's (GOI) Department of Biotechnology (DBT) and the U.S. National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS), and Office of AIDS Research (OAR). CRDF Global administers and oversees the funding from the U.S. government.

Please visit Report India website for additional studies at www.reportindia.org


RePORT India Annual Meeting, 2023, New Delhi

RePORT Indonesia

RePORT Indonesia is part of the ongoing government-to-government partnership between the National Institutes of Allergy and Infectious Diseases (NIAID), and Health Policy Agency or which is formerly known as BKPK, Ministry of Health, Republic of Indonesia. Indonesia is collaborating with RePORT International through the Indonesia Research Partnership on Infectious Disease (INA-RESPOND) project, funded by the U.S. NIH/NIAID and the Indonesia MOH/BKPK. This existing partnership between the two governments supports a network of academic and research institutions and 21 hospitals to conduct research on infectious diseases. The Indonesian MOH has identified TB as a national priority disease area.

Lead by Dr. Erlina Burhan as Principal Investigator, the Indonesia network has completed a cohort study on Tuberculosis called Tuberculosis Research of INA-RESPOND on Drug Resistance (TRIPOD). This study has been harmonized with the RePORT International Common Protocol for collecting data and biospecimens using standardized methods and agreed upon time points. Drug susceptible and multi-drug resistant (MDR) patients were followed from commencement to end of treatment for drug sensitive patients and for two years for MDR patients. The first site activation was in January 2017 and enrollment completed in November 2018 with follow-up of the last participant concluding in April 2021. This study involved 7 TB referral hospitals on the islands of Sumatera, Java, Bali, and Sulawesi as well as 5 additional

laboratories for microbiological testing.

RePORT Indonesia Institutions:

1. H. Adam Malik Hospital, Medan, North Sumatera
2. Persahabatan Hospital, Jakarta, DKI Jakarta
3. Dr. Kariadi Hospital, Semarang, Central Java
4. Dr. Sardjito Hospital, Yogyakarta, Central Java
5. Dr. Soetomo Hospital, Surabaya, East Java
6. Sanglah Hospital, Denpasar, Bali
7. Dr. Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi
8. Microbiology laboratory University of Indonesia, Jakarta
9. Microbiology laboratory Gadjah Mada University, Yogyakarta
10. Center for Health Laboratory, Surabaya
11. Center for Health Laboratory, Semarang
12. Hasanuddin University Medical Research Center Laboratory, Makassar

All of the sites used the same protocol and case report form (CRF). All of the data and

specimens were pooled on INA-RESPOND Secretariat and INA-RESPOND Reference Laboratory for Infectious Disease Research. TRIPOD study aims to get a better understanding of TB case management in Indonesia, especially DR-TB in order to provide evidence-based recommendations for the national tuberculosis programs (NTP). Additionally, data collected from this study will be useful for planning future TB research studies in Indonesia, such as evaluating novel diagnostic tests, evaluating markers of response to treatment, and identifying new therapies.

The primary objective of TRIPOD is to estimate the proportion of MDR TB amongst new and previously treated TB cases. Based on this objective we found that amongst 447 participants with complete AFB, GeneXpert MTB/RIF, and sputum culture results, 58.2% were classified as newly diagnosed TB and 41.8% as previously treated TB cases. Mono resistance was more frequent in newly diagnosed TB versus previously treated TB cases (32.8% vs. 14.6%). MTB resistant to either rifampicin or isoniazid dominated the mono- and poly-resistant subgroups for both newly diagnosed TB (73.7% and 61.5%) and previously treated TB (64.3% and 88.9%) cases. Three (5.2%) pre-XDR isolates were detected in newly diagnosed TB cases and nine (9.4%) in previously treated TB cases.

The Histoplasmosis Among TB Patients manuscript is now under consideration in a peer-reviewed journal. Meanwhile, other findings such as TB treatment outcomes are being analyzed. We plan to utilize a battery of specimens collected in the TRIPOD study for further examination. We realize that one way to reach this purpose is to collaborate with other members of REPORT consortia. However, the material transfer agreement (MTA) process in Indonesia remains challenging. Thus, in-country capacity building in performing genomic, metabolomic, and proteomic assays for tuberculosis will be the best alternative so that we could examine the specimens at our reference laboratory.

LIST OF PUBLICATIONS:

1. Burhan E, Karyana M, Karuniawati A, Kusmiati T, Wibisono BH, Handayani D, Riyanto BS, Sajinadiyasa IGK, Sinaga BYM, Djaharuddin I, Indah Sugiyono R, Susanto NH, Diana A, Kosasih H, Lokida D; Siswanto; Neal A, Lau CY, Siddiqui S. Characteristics of Drug-sensitive and Drug-resistant Tuberculosis Cases among Adults at Tuberculosis Referral Hospitals in Indonesia. Am J Trop Med Hyg. 2022 Oct 17;107(5):984-991. doi: 10.4269/ajtmh.22-0142. PMID: 36252800; PMCID: PMC9709011.
2. Karuniawati A, Burhan E, Koendhori EB, Sari D, Haryanto B, Nuryastuti T, Gayatri AAAY, Bahrun U, Kusumawati RL, Sugiyono RI, Susanto NH, Diana A, Kosasih H, Naysilla AM, Lokida D, Neal A, Siddiqui S, Lau CY, Karyana M. Performance of Xpert MTB/RIF and sputum microscopy compared to sputum culture for diagnosis of tuberculosis in seven hospitals in Indonesia. Front Med (Lausanne). 2023 Jan 20;9:909198. doi: 10.3389/fmed.2022.909198. PMID: 36743681; PMCID: PMC9896521.

RePORT Korea

Institution

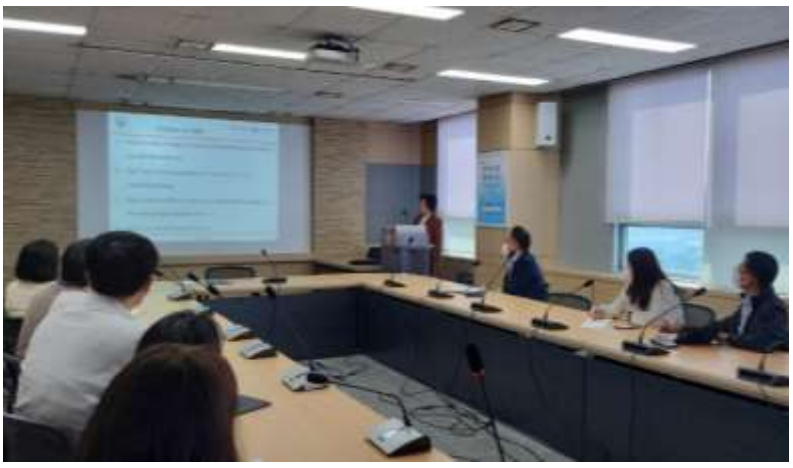
RePORT Korea started as part of a collaboration between the National Institute of Infectious Disease (NIID) of the Korea National Institute of Health (KNIH) and the National Institute of Allergy and Infectious Disease of the United States. The Division of Bacterial Disease Research of the Center for Infectious Disease Research under the NIID oversees RePORT Korea. The ultimate aim of RePORT Korea is to build a foundation for multinational collaboration to facilitate communication among tuberculosis researchers. To achieve this, RePORT Korea is providing opportunities for researchers and institutes within the field to participate in international collaborative programs.

Principal Investigator

Seonghan Kim, Ph.D., Director of Division of Bacterial Disease Research

Project Descriptions

RePORT Korea is running two projects to contribute to the consortium. For an international collaborative research (Project I), RePORT Korea concluded the agreement with De La Salle Medical and Health Science Institute (DLSMHSI) to conduct a cohort study. The study will identify biomarkers for distinguishing patients with latent tuberculosis infection (LTBI) and active disease and predicting the development of tuberculosis in household contacts of patients with active tuberculosis. The NIID is financially supporting this three-year project, and the Division of Bacterial Disease Research is in charge of this collaborative research. As part of this, RePORT Korea organized a workshop for the researchers of DLSMHSI about next-generation sequencing analysis. It also organized a seminar introducing the tuberculosis research infra of Korea Disease Control and Prevention Agency (KDCA) including the Biosafety level 3 facility. The second project (Project II) is aimed at connecting the cohort study of pulmonary tuberculosis, which has been performed in Korea, to RePORT-international to share its data and resources. PPD® has reviewed the manual of operation and procedure as requested by RICC. In addition to a review of the protocol, purpose and the design of the study, any issues in data harmonization will be discussed. RePORT Korea is expecting that this cohort study will provide valuable markers for shortening the treatment period.



Project I

Title: Biomarkers for predicting the development of active disease in household contacts with latent tuberculosis infection

Background and Aim: Patients with LTBI may be reservoirs of active TB. To achieve the goal of END-TB, it is essential to reduce the number of patients with LTBI who progress to active disease through accurate identification and prompt treatment. Therefore, it is crucial to discover biomarkers that can distinguish patients with active TB from those with LTBI and healthy controls and predict the progression of latent TB infection to active disease.

Study Design and Methods

- Establish Cohorts A (Active TB, 300 patients) and B (LTBI and healthy household contacts, 300 individuals) to collect specimens and clinical data of the participants
- Analyze the concentrations of the target cytokines/chemokines in the collected plasma using the Luminex assay, and the levels of mRNA expression using qRT-PCR and the PAX gene
- Share collected specimens with the Korea National Institute of Health for the study of the metabolites as biomarkers

Research Period: November 25. 2022 ~ December 31. 2024

Institute: De La Salle Medical and Health Science Institute (PI: Charles Y. Yu)

Funding: Korea National Institute of Health, Korea Disease Control and Prevention Agency

Project II

Title: Cohort Study of Pulmonary Tuberculosis (COSMOTB)

Background and Aim: The Korea National Institutes of Health performed a cohort study in Korea to develop strategies to shorten the duration of anti-TB treatment. Despite the various difficulties in conducting cohort studies in Korea, this observational study continues to provide scientific data for policymakers. RePORT Korea intends to share data with other participants in the consortium and contribute to developing new technologies for the END-TB Strategy. We aimed to enroll more than 1000 patients with active pulmonary TB in Korea and identify biomarkers to predict their prognosis. Recently, the efficacy of anti-TB treatment in patients with INH-resistant tuberculosis was evaluated within this cohort study. This provided scientific evidence for the update of the "Korean guidelines for tuberculosis (4th edition)." The specimens and samples collected from this cohort will be used for the intramural study by the KNIH to identify biomarkers for predicting anti-TB treatment outcomes. RePORT Korea has requested the executive committee to determine whether this project could be recognized as part of its activities.

Study Design and Methods

- Identify the various clinical and socioeconomic factors that affect the outcomes of anti-TB treatment
- Identify the factors associated with outcomes of anti-TB treatment
- Enroll 1000 patients (aged ≥19 years) with pulmonary tuberculosis
- Collect relevant clinical and epidemiological data prospectively
- Collect specimens (Blood, sputum, and urine) during selected visits

RePORT Philippines

RePORT Philippines has two sites – the University of the Philippines Manila – National Institutes of Health (UPM-NIH) and the De La Salle Medical and Health Sciences Institute (DLSMHSI). Both sites have their own individual parent protocols which incorporate the RePORT Common Protocol. UPM-NIH started study enrolment in June 2018, while DLSMHSI started enrolment in April 2019.

UNIVERSITY OF THE PHILIPPINES MANILA - NATIONAL INSTITUTES OF HEALTH – RePORT Team

Co-Principal Investigators: Marissa M. Alejandria, MD, MSc, John Carlo Malabad, MD-PhD; Esterlita Uy, MD, MPH
Laboratory Team: Dana Kamylle Santos; Christine Mae dela Cruz; Marck Anthony Sargento, Guia Jobelle Orduna
Data Management Team: John Benedict Carandang, Noe Cenal
Field Team: Arly Joyce Catoy, Nerissa Lapitan, Marilyn Epe
Administrative Team: Mina Capistrano, Rodel Morales, Brendalyn Red

LONG-TERM OUTCOMES OF DIAGNOSED TUBERCULOSIS CASES IN THE PHILIPPINES

Background: The Philippines is among the top high burden countries for TB, MDR-TB and TB-HIV co-infection. Results from the 2016 National TB Prevalence Survey estimates a prevalence of bacteriologically confirmed pulmonary TB in those ≥15 years of 1,159 per 100,000 (95% C.I. 1,016—1,301). This translates to ~1 million Filipinos having pulmonary TB disease. According to the Global TB Report 2021, Philippines remains as the fourth country with the highest number of TB incident cases. In 2020, it was estimated that 591,000 individuals developed active TB disease in the country, with 6,279 laboratory-confirmed cases of MDR/Rifampicin-resistant (RR) TB. No studies have been conducted on the long-term outcomes of patients diagnosed with TB in the Philippines.

Assessing the long-term outcomes of TB can provide useful information in determining the effectiveness of current treatment regimens in the National Tuberculosis Program (NTP) and identifying populations who may have drug resistance or are vulnerable to developing recurrence of TB. Furthermore, long-term follow-up of household contacts of these patients will also provide data on characteristics which make them vulnerable to develop infection and subsequent disease. Results from the study will be useful as it will guide future programmatic implementation of the NTP.

Objectives: To determine the long-term (at least two years) outcomes of TB cases

1. To determine the rates of recurrence of TB, 3 months after the end of treatment (microbiologically-confirmed and clinically diagnosed cases) up to the end of the study period (Cohort A)
2. To determine the outcomes of exposed individuals to diagnosed TB cases within two years of the diagnosis of the index case (Cohort B)
3. To provide specimens to RePORT consortia biomarker researchers and their collaborators to achieve a better understanding of the prognosis of TB disease and the pathogenesis of progression from TB exposure to disease. (Cohorts A and B)

4. To identify possible factors and biomarkers that may be associated with various tuberculosis states (LTBI, recurrent TB, active disease and disease progression) (Cohorts A and B)
5. To determine the strains of *M. tuberculosis* in Filipino patients and household contacts who eventually develop tuberculosis using molecular epidemiologic techniques and if possible, compare with previous isolates (Cohorts A and B)

Site: Study participants were recruited in the rural health units of the municipality of Los Baños, Laguna in the Southern Tagalog region. Los Baños has a population of 126,280 as of 2020, and is located ~63 kilometers south of Manila. Population density is at 2,329 inhabitants per square kilometer. Prior to the study initiation, from September 2015 to August 2017, there were 604 adults and 309 children diagnosed with TB in Los Baños, Laguna.

Preliminary Data: Active recruitment for Cohorts A and B ended in November 2022. Data analysis of RePORT participants is ongoing, while completion of the two year follow-up is also ongoing. For RePORT Cohort A, 581 active TB patients have been enrolled (82% treatment naive, 18% with past history of treatment). Majority were adults with only 10.5% less than 15 years-old. Favorable outcome is reported for 355 participants (133 bacteriologic cure, 222 treatment complete/indeterminate bacteriologic status) while there were 4 bacteriologic failures, 2 bacteriologic relapse cases and 19 deaths as of February 2023.

For RePORT Cohort B, 686 household contacts of active TB patients have been enrolled, 38% of whom were less than 15 years-old. A total of 323 participants have completed the 24-month follow-up period, 262 are still ongoing follow-up. 230 developed LTBI while 45 progressed to active TB as of February 2023.

All specimens collected from Cohorts A and B participants were sent to the central laboratory of the UPM-NIH for processing, testing and biobanking.

REPORT CROSS-CONSORTIA PROJECTS:

RePORT Philippines is actively collaborating with other members of RePORT International Consortium for several research projects.

Latent TB Infection and COVID-19 Infection

1. Impact of Latent TB Infection and Trained Immunity on Susceptibility to SARS-CoV-2 Infection in India and Philippines
   Funding: CRDF Global

   This is a collaborative project between RePORT Philippines (UPM-NIH), RePORT India (JIPMER) and Rutgers University. The study aims to (1) determine the seroprevalence of COVID-19 in household contacts of pulmonary TB patients stratified by LTBI status (India), (2) determine the prevalence of LTBI in patients with confirmed COVID- 19 infection and their household contacts and the association of LTBI with COVID-19 severity (Philippines), and (3) examine trained immunity in monocytes and NK cells in individuals of known SARS-CoV-2 status stratified by the presence or absence of LTBI.

   To date, we have recruited 123 index COVID-19 patients of varying severity and 79 of their household contacts. Target sample size is 300 COVID-19 patients and 250 of their household contacts from the Philippines and 300 RePORT Cohort B participants from India. Serum specimens are being prepared for shipment to Rutgers University for SARS CoV-2 antibody testing.

Epidemiology of TB

1. Data Harmonization –
   Funding: CRDF Global

   RePORT Philippines partners with all the RePORT International Consortium members for the Data Harmonization project (Epidemiologic factors associated with TB treatment outcomes across RePORT International Consortia), which aims to determine the impact of key non-communicable and communicable diseases, such as Diabetes, HIV infection, malnutrition, etc., on TB treatment outcomes and recurrence using data from multiple RePORT International consortia. Data mapping is ongoing.

Biomarker discovery and validation in TB in Adults

1. Dynamic detection of cytokines by liquid chip technology to evaluate their utility in predicting response to anti-tuberculosis treatment
   Funding: CRDF Global

   This is a collaborative project between RePORT Philippines (UPM-NIH) and RePORT China which aimed to determine the concentration changes of select cytokines among active TB patients before treatment initiation, at 1 month and 2 months after treatment initiation and at the end of treatment, and to correlate these with the outcomes of the patients. The project will help evaluate the use of candidate cytokines for early prediction and evaluation of response to standard anti-TB treatment and for prognosis of TB cases.

   The target sample size 150 participants with active TB has been reached (October 2022). Of the 150 study participants (77 from RePORT Cohort A site, 73 from non-RePORT site), 123 (82%) had favorable outcomes (cured). Four participants had unfavorable outcomes (2 treatment failures and 2 deaths), while 23 were withdrawals (12 with

incomplete specimens). Complete analysis is pending while we await the completion of the cytokine assays.

2. TB RiCC Biomarker Protocol: Analysis of Host Biomarkers Associated with Adverse Tuberculosis Treatment Outcomes Across RePORT International Sites
   Funding: CRDF Global

   This cross-consortium study of RePORT International sites involves analysis of samples from RePORT International Cohort A participants with adverse TB treatment outcomes. It aims to expand the validation studies of host biomarkers associated with TB treatment failure proposed at each RePORT site, cross-validate the biomarkers in samples across RePORT International Consortia, and identify a biomarker of "cure" using a discovery-based approach. This will employ newer technologies, such as Luminex, Fluidigm, NanoString and RNA-seq platforms for biomarker discovery and validation using plasma and PAXgene samples. The study also involves capacity building and training of young investigators on the newer biomarker technologies.

3. Biomarker discovery for predicting the development of active disease in household contacts/subjects with latent tuberculosis infection
   Funding: Korea NIH

   This is a collaboration between RePORT Philippines (DLSMHSI and UPM NIH) and RePORT Korea, through the Korea National Institutes of Health which aims to determine and discover biomarkers to discriminate active TB (children and adult; drug-susceptible and drug-resistant) from LTBI and healthy controls and predict progression of latent TB infection to active disease using multiplex analysis of plasma samples and targeted transcriptomic analysis of PAXgene tube samples from RePORT Cohorts A and B. Currently, training and capacity building on the laboratory assays to be employed are ongoing in both RePORT Philippines sites.

TB in Children

1. Urine metabolomic characterization among children with different Tuberculosis status
   Funding: CRDF Global

   This shovel-ready research project is a substudy under RePORT Philippines that aims to determine the metabolomic profile of children with active TB and LTBI and those who converted from healthy or LTBI to active TB using urine samples collected from RePORT Philippines Cohorts A and B pediatric participants. Liquid Chromatography - Mass Spectrometry and Nuclear Magnetic Resonance assays were performed to characterize the different urine metabolomes among children. Currently, all lab assays have been done, and data analysis is ongoing.

2. Characterization of inflammatory markers among children with different TB status and on conversion to active TB
   Funding: Philippine Council for Health Research and Development

   This ongoing substudy on TB in children under RePORT Philippines involves multiplex analysis of plasma samples to describe the cytokine/chemokine levels that can be used as

biomarkers to discriminate active TB from LTBI and healthy controls and predict progression of latent TB infection to active disease.

3. Association of Vitamin D levels and Vitamin D receptor epigenetic changes and TB conversion among children exposed to adult TB household members
   Funding: Philippine Council for Health Research and Development

   This study that aims to describe the Vitamin D status and the epigenetic characteristics of the Vitamin D receptor (VDR) gene among children who are household contacts of active TB cases in RePORT Cohort A. Plasma and PBMC samples will be subjected to Vitamin D level determination and VDR gene methylation analysis to look for association between Vitamin D levels and VDR epigenetic changes and progression to active TB among children. The laboratory assays are set to start this August 2023.

REPORT PHILIPPINES PHASE II

Phase I of RePORT Philippines UPM-NIH and DLSMHSI ended on February 2023 and April 2023, respectively. With this, the team is preparing for Phase II research activities.The RePORT Philippines Phase II will involve the use of the biobanked samples from Phase I to conduct studies, such as (i) transcriptomic profiling and analyses of LTBI and active drug sensitive and drug resistant TB (ii) biomarker discovery studies among adult and pediatric TB cases, and (iii) genomic and molecular epidemiologic studies. Two proposals have been submitted by UPM-NIH in collaboration with Rutgers University and Vanderbilt University in response to the U.S. NIH - PCHRD Collaborative Research Call for Tuberculosis (CoRe TB) proposals.

DE LA SALLE MEDICAL AND HEALTH SCIENCES INSTITUTE

Project Title: Community Approach to Control and Halt Drug-Resistant Tuberculosis (COACH DRTB)
Principal Investigator: Charles Y. Yu, MD, MSc.
Significance of the Study: The DLSMHSI COACH – DRTB Strategy is by conducting a local groundbreaking project involving intensified case finding utilizing the Kagabay community workers to identify active DRTB cases and latent TB among DRTB contacts of bacteriologically confirmed cases with assessment factors for poor treatment outcome. The project also focused on the social value of the study and emphasized that the monitoring of adherence is an innovation involving Barangay (community) Health Workers (BHW) as front liners and with patient advantages compared to DOT.
In support of RePORT International, the study collected patient specimens for future biomarkers studies.

General Objective: To determine the effectiveness of COACH-DRTB strategy in the detection and treatment of DRTB. This project aims to:

1. To determine the treatment success rate among the active DRTB Cases after completion of treatment.
2. To determine the relapse rate of treated patients observed 2 years post-treatment.
3. To determine the incidence of active TB disease among household contacts of patients with DRTB observed within 2 years.
4. To determine the factors associated with positive outcomes (cured, treatment completed).

Methodology:
The project is a prospective observational study which consists of three phases as follows:
Phase 1. Engagement Phase: Upon site selection, the project conducted training to the identified community health workers and volunteers using the Kagabay Module.
Phase 2. Execution Phase: Kagabay health workers are deployed to selected sites for active case finding using a standard questionnaire. Testing of presumptive DRTB and household contact cases is done at DLSMHSI – Center for TB Research and the peripheral DOTS facility (City Health Office) according to the NTP Manual of Procedures and Common protocol implementing guidelines.
The Kagabays were trained regularly based on DOH guidelines. Relative to this, the Kagabays were also trained on the adaptive guidelines in treating TB cases with COVID-19 correlation.
Eligible participants are classified into two main groups.
Cohort A is composed of presumptive cases who are bacteriologically confirmed DRTB based on positive Direct Sputum Smear Microscopy, TB Culture or GeneXpert result.
Patient-centered approach was followed based on the patient's preferred site of treatment. Patients may opt to choose between full *ComPcare* (community-based, with Kagabay as treatment partner), *partial ComPcare* (Intensive phase treatment at the facility followed by community-based DOT with Kagabay) and facility-based options.
Cohort B is composed of persons who share an enclosed space, such as the household, a social gathering place, workplace or facility, for extended periods within the day with the index case during the 3 months before commencement of the current treatment episode.
Phase 3. Evaluation Phase: Assessment of treatment outcomes in Cohort A is done after successful completion of treatment (cure or complete) with a post-treatment follow up every 6 months for 2 years
Among Cohort B, development of active TB disease is assessed every 6 months for 2 years.
Outcome predictors such as patient treatment success rate among the active DRTB cases after completion of treatment, the factors associated with positive outcomes (cured, treatment completed), the relapse rate of treated patients observed 2 years post treatment and the incidence of active TB disease among household contacts of patients with DRTB observed within 2 years will be evaluated.
Site of the Study: Eight (8) high burden communities in the province of Cavite in the Southern Tagalog region, including City of Dasmariñas, Silang, Gen. Mariano Alvarez, City of Imus, City of Bacoor, Trece Martires City, City of General Trias and Naic, are involved in the study.
Interim Result: From April 2019 to April 2022, the project was able to recruit a total of 353 participants. 159 Cohort A and 163 Cohort B consented with the RePORT Common Protocol. As of June 30, 2023 all participants from Cohort A have completed their prescribed treatment and are now under post treatment monitoring. 144/159 of the Cohort A has an evaluable outcome. Treatment success rate is at 88.9% with Cured and Treatment completed as majority of the outcomes. 5 (3.5%) were lost to follow-up, 2 (1.4%) treatment failure and 9 (6.3%) died while on treatment. 15/159 of the participants' outcomes were not evaluated due to withdrawn participation (8) and transfer of treatment facility (7).

For the post treatment monitoring, 33 participants completed the 2 years follow up with no signs of active TB infection, 5 have died and 3 cases of relapse were captured between 6 to 18 months PTFU while 5 Cohort A were lost to follow up.
For Cohort B, 26 participants are still under monitoring and are expected to be completed by February 2024. 121/163 has an evaluable outcome. 110 of the cohort has completed the 2 years monitoring period without developing TB infection, 1 died related to COVID, 2 were lost to follow-up and 8 had a TB activation in which half are children under 5 who were clinically diagnosed.

Project Collaborations using the RePORT Banked specimens:

- **A molecular epidemiologic analysis of drug resistant mycobacterium tuberculosis isolates derived from the 3rd Philippine TB drug resistant survey 2018 and community-based study (MERIT TB).**

Started in May 2021**,** this ongoing joint project between DLSMHSI and Research Institute for Tropical Medicine (RITM) sponsored by the Department of Science and Technology (DOST) aims to identify the molecular subtypes or strains of drug resistant *M. tuberculosis* derived from the 3rd Philippine TB Drug Resistance Survey of 2018 and the community-based study in Cavite using whole genome sequencing and to identify possible association of specific molecular subtypes or strains of *M. tuberculosis* that are multidrug resistant with specific features of the disease and specific demographic characteristics of the host. This will provide a more comprehensive description of the circulating strains of drug-resistant *M. tuberculosis* in the Philippines.

- **Biomarker discovery for predicting the development of active disease in household contacts with latent tuberculosis infection**

Sponsored by Korea National Institute of Health this project will utilize the banked samples of UPM-NIH and DLSMHSI which aims to discover biomarkers, such as

cytokines/chemokines, mRNA signatures and metabolites that can discriminate between active TB, latent TB infection and healthy individuals**.** This project which started in January 2023 is going to be implemented for 25 months.

Future Project Plans

Phenotypic testing through whole genome sequencing is in the pipeline using the banked isolates with plans to consider new sets of sample collection to add into the available specimen.

RePORT South Africa

Research Consortium:

The RePORT South Africa Consortium comprises a network of investigators from 6 South African and 4 US institutions.

SA Institutions and Investigators:

University of Cape Town (UCT), including the South African Tuberculosis Vaccine Initiative (SATVI) and Centre for Infectious Diseases Research in Africa (CIDRI-Africa) sites (Hatherill; Scriba; Tameris; Meintjes; Wasserman); University of Cape Town Lung Institute (UCTLI) (Dheda; Dawson; Zar (Red Cross Children's Hospital)); Stellenbosch University (SUN), Immunology Research Group (SUN-IRG) (Walzl; Malherbe; Warren); Africa Health Research Institute (AHRI) (Leslie); University of Pretoria (UP) (Fourie); University of the Witwatersrand, Perinatal HIV Research Unit (PHRU) (Martinson; Moloantoa; Varieva).

US Institutions and Investigators:

Vanderbilt University Medical Center (Sterling; Duda; van der Heijden); Brigham and Womens' Hospital (BWH) (Suliman); Colorado State University (CSU) (Belisle; Dobos) and University of Washington (UW) (Cangelosi; Wood - consultants).

The consortium includes 8 clinical research sites (SATVI; CIDRI-Africa; UCTLI; Red Cross Children's Hospital (via UCTLI); SUN-IRG; AHRI; UP; PHRU) and 6 analytic laboratories (SATVI; UCTLI; SUN-IRG; AHRI; BWH; CSU).

RePORT Phase I:

RePORT SA Phase I was a joint venture between the South African Medical Research Council (SAMRC), with support from the South African Department of Science and Technology (DST) and Department of Health (DOH), and with co-funding by the U.S. Division of AIDS (DAIDS), National Institute for Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), and the Office of AIDS Research (OAR). In 2015 the SAMRC, as part of this initiative, established the SAMRC TB HIV Collaborating Centers, which exclusively competed through a request for application (RFA) process for a RePORT SA award. Five sites were awarded and investigators were funded to enroll subjects from their existing parent protocol with compliance to the RePORT International Common Protocol, in which eligible subjects were co-enrolled, including active TB patients and latently TB infected (LTBI) household contacts. To date, RePORT SA investigators have secured 11 sub-grants leveraged by RePORT funding and published 27 peer-reviewed papers supported by RePORT.

RePORT Phase II:

RePORT South Africa Phase II strengthens the global RePORT effort by: (1) expanding the RePORT South Africa network to include new prospective cohorts and scientific collaborators in a consortium of 6 SA and 4 US institutions; and (2) evaluating a range of biomarker

approaches to detect symptomatic and subclinical TB disease.

Project Roles:

The Project Core at the University of Cape Town administers the logistical needs of investigators, clinical sites and laboratories. The Leadership Group (Drs Hatherill, Sterling, Walzl, Scriba, Zar), comprising the leaders of the Project Core, Data Harmonization, Diagnostic, Prognostic, and Pediatric Biomarker Work Packages, will work through the network of 8 clinical sites to implement prospective cohorts based on the RePORT Common Protocol and associated data standards. The consortium builds upon the existing RePORT SA network, successful partnerships with US institutions (Vanderbilt, Colorado State, Brigham and Women's Hospital, University of Washington) and advanced SA biomarker laboratories (SATVI, UCTLI, SUN-IRG, AHRI), and will be supported by a central Biorepository (SUN-IRG) and Data Center (PHRU) harmonized with international RePORT standards.

Study Design:

Screening for entry into Common Protocol Cohorts A (TB patients) and Cohort B (Mtb-exposed individuals) has been identified as an opportunity to test biomarker approaches to detect symptomatic TB, among individuals with symptoms consistent with active disease; and subclinical and incipient TB, among household contacts and others at risk for progression to active disease. Performance of novel proteomic, metabolomic, transcriptomic, and Mtb DNA biomarkers will be tested at 7 research laboratories, using standardized whole blood, serum, urine, sputum and oral swab sample sets, in study populations that include adults, children, and people living with HIV. The most promising biosignatures, benchmarked against established Target Product Profiles for triage, diagnostic and prognostic TB tests, will be evaluated head-to-head. To optimize statistical power for analyses, the project will leverage data and stored samples previously collected under the Common Protocol (RePORT SA1); stored samples from aligned cohorts (GC6, CORTIS, PREDICT); and new samples from ongoing recruitment (RePORT SA2), to generate research outputs during the 3-year grant cycle. Data harmonization across these three sources of data and specimens will lay a solid foundation for future analyses. To date, Cohort B is almost fully enrolled and recruitment into Cohort A is ongoing.

Aim 1: Expand and strengthen the RePORT South Africa consortium. The existing network of experienced, multi-disciplinary RePORT SA investigators will continue to recruit prospective cohorts using standardized data and sample collection methods described in the RePORT Common Protocol, and will collaborate with international RePORT consortia in observational TB research, supplemented by 2 new SA institutions and 3 new US laboratories with complementary TB biomarker capacity.

Aim 2: Establish a central RePORT South Africa Biorepository and harmonized central Data Center. Participant samples and data already collected through the RePORT Common Protocol, through existing large cohorts aligned to the Common Protocol (GC6, CORTIS, PREDICT), and through future RePORT Common Protocol recruitment, will be harmonized using RePORT International data standards. The existing PHRU Data Center will continue its mandate; and the Vanderbilt team will facilitate data harmonization across the SA study sites and with RePORT cohorts in other countries. A new central Biorepository will be established at Stellenbosch University for storage of prospectively collected samples.

Aim 3: Evaluate tests for diagnosis and triage of symptomatic active TB disease. Candidate biosignatures will be evaluated in symptomatic adults and children, with and without HIV-coinfection, and in HIV-exposed uninfected (HU) children. We will perform head-to-head comparisons of the most promising biomarkers in symptomatic patients at screening for entry into RePORT Cohort A.

Aim 4: Evaluate tests to identify individuals with undiagnosed subclinical and incipient TB disease. Candidate biosignatures will be evaluated in adults with household TB exposure and

other risk factors for progression to disease. Promising biomarkers identified for diagnosis of symptomatic TB in Aim 3 will also be tested for detection of microbiologically-confirmed, subclinical (asymptomatic) TB; and progression from incipient to active TB disease. We will perform head-to-head comparisons of the optimal diagnostic biomarkers in individuals with household TB exposure and other risk factors at screening into RePORT Cohort B.

Key Progress Metrics:

Table 1: Recruitment metrics and TB case accrual by site

Cohort A	**Total enrolled (100%)**	**Last participant enrolment**	**Completed follow-up (%)**	**Baseline Prevalent TB cases**	**Recurrence/ Relapse cases**	**LTFU**
AHRI	303	30 Jan 2023	82 (27%)	101	2	4
UP	60	30 Jan 2023	12 (20%)	38	(1)	(30)
SUN	150	16 Sep 2022		23	0	10
UCTLI	300	30 Mar 2023	1 (LTFU)	53	0	8
PHRU	32	15 Sep 2021	32 (100%)	22	0	0
REACH	120	29 Sep 2022	77 (64%)	39	0	18
Cohort B	Total enrolled	Last enrolment date	Completed follow-up (%)	Baseline Prevalent TB cases	Incident TB cases	LTFU
SATVI	450	8 Jun 2022	444 (99%)	40	5	3
SUN	167	23 Sep 2022		4	0	5
PHRU	365	6 Apr 2022	340 (93%)	9	4	(0)

Preliminary Data:

Preliminary biomarker data will be presented at the RePORT SA annual meeting in Pretoria, 19-20 October 2023.

List of Associated Projects:

Table 2: Sub-studies listed by funder, title and PI.

Funder	Short Title	Grant Title	PI Name(s)
CRDF	EDICT	Enhancing diagnostics and improving outcomes in childhood Tuberculosis G-DAA3-17-63192-1	Lala
CRDF	TBnD	Molecular Signatures of Tuberculosis-Diabetes Interaction G-OISE-17-63459-1	Martinson
CRDF	PARTHISA	Pregnancy associated immune responses to TB and HIV in India and South Africa DAA9-19-65349-1	Martinson
CRDF	MDR TBM PK	Pharmacokinetic Assessment of MDR-TB Drugs in the Treatment of TB Meningitis	Variava

Funder	Short Title	Grant Title	PI Name(s)
		DAA9-19-65356-1	
NIH (R01)	NA	Immunogenetic predictors of active and incipient TB in HIV-negative and HIV positive close TB contacts	UCT Scriba (PI Sterling)
CRDF	NA	Towards a global TB biomarker: Comparison of small transcriptomic signatures to predict, diagnose and monitor TB disease in Brazil and South Africa	Kimbung
CRDF	NA	Host RNA expression for diagnosis and monitoring of pediatric TB in Africa and India DAA3-18-64086-01/CRD0001	Workman
CRDF CFAR	NA	Immune activation and dysglycemia in tuberculosis patients with and without HIV	van der Heijden Leslie Koethe
CRDF	NA	TB-RICC Laboratory Network	Scriba
CRDF	RICC	RePORT International Coordinating Center (RICC)	Hatherill
SAMRC	NA	Addendum to Funding Agreement from SAMRC to K-RITH. Lesion heterogeneity in human pulmonary tuberculosis and additional work to evaluate the relationship between hyperglycemia and TB treatment	Leslie
CRDF	NA	Gene signatures for monitoring treatment response and predicting treatment outcome among tuberculosis patients in Brazil [G-202212-69603]	Mendelsohn
CRDF	HHC OS	Oral Swab Screening for TB Among Household Contacts of TB Cases [G-202212-69598]	Cangelosi
CRDF	STARS	Subclinical TB assessed by RNA Sequencing Exploration of Functional and Immune Status of Lungs Post tuberculosis	Scriba
CRDF	Post TB		Malherbe Tameris

LIST OF PUBLICATIONS SUPPORTED BY REPORT FUNDING:

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RePORT Uganda

The implementation of RePORT in Uganda is a positive step towards advancing TB research and improving healthcare in the country. The RePORT consortium is welcome to Uganda, and the teams look forward to implementing the Common Protocol towards advancing TB research and innovation.

RePORT Uganda team will be led by Prof Moses Joloba. He is a physician researcher with expertise on infectious diseases diagnostics and program implementation using both conventional microbiology and modern molecular approaches. He is the chair of the World Bank funded East African Public Health Laboratory-networking group that aims to establish in East Africa, high quality, accessible public health laboratories for the diagnosis and surveillance of TB and other communicable diseases. He has successfully competed for extramural research support (obtained 10 grants so far) and published over 230 peer-reviewed research articles. He is currently leading a team of researchers evaluating novel diagnostics for Tuberculosis in children under 5 years and adult populations. He is also the chair of the Supranational Reference Laboratory (SRL) reference laboratory in Uganda which implements WHO policy guidance on TB diagnostics and Laboratory norms and standards in Uganda and beyond while respecting relevant national laws and regulations. The SRL works with the National TB and Leprosy program (NTLP) which oversees all TB program in Uganda.

A number of sites will be involved in RePORT Uganda.

Iganga-Mayuge Health and Demographic Surveillance Site (IMHDSS)

IMHDSS serves as a population-based research platform where demographic and health data are collected from a defined population over time. IMHDSS will contribute valuable data for TB research and surveillance efforts. The site covers a contiguous and clearly demarcated area of 155km^2, a part of Iganga and a part of Mayuge districts. It is made up of 65 villages in seven sub-counties and it is enclosed by 16 health centres and a hospital. Currently, the HDSS covers a population of 90,000 people from 17,000 households, about 59% living in rural areas.

*Figure SEQ Figure * ARABIC 1 Areas covered by Demographic surveillance Survey*

Jinja Regional Referral Hospital

JRRH As a regional referral hospital for Eastern Uganda, it offers outpatient, inpatients and specialized healthcare services including TB case management. RePORT activities at this site will involve clinical research, patient care, and capacity building. The site is actively enrolling study participants in a number of diagnostic studies including Novel and Optimized Diagnostics for Pediatric TB in Endemic Countries and Accuracy of Novel Diagnostic Tests for Detection of Tuberculosis in Adults (FEND-TB).

Integrated Biorepository of H3Africa Uganda (IBRH3AU)

IBRH3AU is an integrated biorepository at Makerere University College of Health Sciences under the NIH's H3Africa initiative. IBRH3AU provides a resource of well-characterized and annotated high quality biospecimens for future use by researchers as well as trainers. This resource serves both communicable and non-communicable disease researchers in Africa. The ultimate goal of IBRH3AU is to improve the prevention, diagnosis, and treatment of illness and the promotion of health throughout society. All activities are done in adherence to current SOPs and GCLP standards. The quality assurance program covers the pre-analytical, analytical, and post-analytical phases. This is through standard procedures like sample rejection/acceptance, routinely monitored Turn-Around-Time, Internal Quality Controls (IQCs), External quality assessment (EQA) proficiency programs, Blind/Split sample testing, etc. IBRH3AU is currently in its advanced stage preparations for SANAS/SADCAS accreditation. The biorepository is also equipped with state-of-the-art Genomics, Molecular and Immunology laboratories that process biospecimens and add value. IBRH3AU will be key in the long-term storage and shipment of biospecimens collected under the REPORT protocol. IBRH3AU currently supports research studies in East and Central Africa.

*Figure SEQ Figure * ARABIC 2 Aerial view of Jinja RRH and research team*

Figure 3 Storage capacity and areas of Africa served by IBRH3AU

The Genomics, Molecular, and Immunology Laboratories (GMI Labs)
GMI labs are diagnostic, research, and training facilities, focused on both infectious and non-infectious diseases or conditions. The GMI Laboratories provide laboratory services to all healthcare providers, including physicians, researchers, epidemiologists, students, and all healthcare policymakers, for the benefit of patients and the global community. GMI offers quality diagnostic, training, and research services using the most advanced Genomics, Molecular, and Immunology techniques while complying with the ISO 15189:2012 requirements for medical laboratories.

Figure 4 GMI sequencing and diagnostic facilities

CAP-accredited Mycobacteriology Laboratory (BSL-3)
The BSL-3 lab is a College of American Pathologists (CAP) – accredited Biosafety Level (BSL)-3 culture facility. It is a site for multinational tuberculosis research initiatives namely: the Division of AIDS Clinical Trials regional TB diagnostic laboratory (DAIDS/ACTG/RTBDL) and the International Maternal, Paediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network, and the Global Alliance for TB drug development studies. This facility has vast experience in clinical trials including those for novel tuberculosis drugs for treating MDR-TB for example, the laboratory participated in the BPaMZ regimen for MDR-TB treatment. Other clinical trials include those for both susceptible and resistant TB with study numbers in public databases [NCT02410772 (TBTC study 31, S31/A5349), NCT02193776 (NC-005-(J-M-Pa-Z), NCT01380080 (REMEMBER, ACTG 5274), IMPAACT P1078 (DAIDS ID 10732), ISRCTN63579542, NCT02342886 (NC-006-(M-Pa-Z)) among others. It has participated in several diagnostic evaluation studies some of which have made it to WHO policies most recently being the multi- country Xpert ULTRA evaluation study. The CAP accredited BSL-3 offers clinical and research TB diagnostic services according to WHO and international guidelines.

Uganda Supra National Reference Laboratory (SRL) The Uganda National Tuberculosis Reference Laboratory was started as the Uganda Bacteriological Investigation Unit in the late 1950's under the then East African Community. The laboratory participated in anti TB clinical trials and drug toxicities under the then British Medical Research Council (MRC). After the collapse of the East African Community in 1970's, the laboratory reverted to the line ministries. Its name changed to Central Tuberculosis laboratory (CTBL) in 1980's and National Tuberculosis Reference Laboratory in the 1990'S. The Uganda National Tuberculosis Reference Laboratory established under the National Tuberculosis and Leprosy Programme

(NLTP) of the Ministry of Health (MoH) received accreditation from the WHO in April 2013, making it the first SRL in East Africa, and the second in Sub-Saharan Africa to achieve this status. SRL supports the integration of quality TB diagnostic services for the purpose of providing prompt and accurate results to patients according to the International Standard of Care with national laboratory strategic plans, incorporating cross cutting laboratory issues including supply management, specimen transport, and referral and human resource development. SRL aadvocates for TB laboratory worker protection with use of current WHO TB bio-safety recommendations. It supports the development of monitoring and evaluation indicators starting with a good data management system. SRL is part of the National TB and Leprosy Program Uganda (NTLP).

IDI-African Center of Excellence in Bioinformatics & Data-intensive Sciences (ACE)

The Infectious Diseases Institute (IDI), Makerere University's College of Computing & Health Sciences (CHS) in partnership with the US Government National Institute of Allergy and Infectious Diseases (NIAID) and the Office of Cyber Infrastructure and Computational Biology (NIH/NIAID/OCICB) established the African Centre of Excellence in Bioinformatics & Data Sciences, one of the 2 such centres on the African continent. ACE is focused on bioinformatics and data-intensive research in the context of infectious diseases, including TB. It provides expertise in data analysis, informatics, and bioinformatics to support TB research and improve data management.

These sites collectively, create a strong foundation for the RePORT Uganda Chapter, enabling a comprehensive approach to TB research, diagnostics, patient care, and capacity building. The collaboration among these institutions will contribute to significant advancements in TB control and treatment in Uganda.

TB RePORT International Coordinating Center (RiCC 3.0)

Rutgers University, New Jersey Medical School

Dr. Jerrold Ellner serves as Director for TB RiCC 3.0 with Rutgers University as the prime awardee. Dr. Ellner has extensive experience in leading multidisciplinary research at international sites, including cohort studies, diagnostics, immunology, and translational research. TB RiCC 3.0 is comprised of investigators from Vanderbilt University Medical Center; Frontier Science; Johns Hopkins University and FioCRUZ.

TB RiCC 3.0 is charged with the management, development and implementation of RePORT International Consortium wide activities, policies and protocol development and adherence. A public informational website (www.reportinternational.org) will provide information on the networks, leadership, the toolkit for the Common Protocol, past webinars, recent publications and a toolkit for Countries and Sites interested in joining RePORT International.

The Rutgers administrative core (AC) supports Dr. Ellner and his team in the management, governance, and financial activities of TB RiCC 3.0. This includes monitoring operations, work-flow processes, chains of responsibility among investigators/staff, and the regulatory review/approval processes. The Rutgers AC establishes subcontracts, monitors core expenses, processes invoices, and provides plans for managing resources, reallocating funds, and overseeing sub-award spending.

The Rutgers data harmonization team works with Vanderbilt and Frontier to harmonize data, clinical coordination, and validation across the many international sites. Under Phase 2 of TB RICC - this team has worked to harmonize data cross six RePORT networks. This effort has demonstrated the ability to harmonize cohorts of Index Cases and Close Contacts for a variety of epidemiologic, translational and biomarker protocols. For TB RICC 3.0, a data hub including Rutgers, Vanderbilt University Medical Center, and Frontier Science was created. The TB RICC 3.0 data hub will review, monitor, and provide data quality assurance review of the data from RePORT networks. The data hub will also establish a "portal dashboard" that will be a consortium collaboration hub, study tracking tool, data index, and resource library for sites, networks, and other LG-approved entities.

Vanderbilt University Medical Center

Vanderbilt University Medical Center (VUMC) in Nashville, USA, also shares in the leadership of the RePORT International Coordinating Center. Led by infectious diseases physician scientist and RICC co-PI Dr. Timothy Sterling, the Vanderbilt team includes co-investigators in epidemiology and clinical research informatics, as well as experienced project coordinators and data managers.

Vanderbilt has a long history of participation in RePORT as a collaborating data center for both RePORT Brazil and RePORT South Africa. Areas of scientific focus in RePORT-Brazil include TB/HIV, TB/diabetes, drug-resistant TB, progression from *M. tuberculosis* infection

to TB disease, and resistance to *M. tuberculosis* infection after TB exposure. All of these studies build upon strengths in observational cohort studies, epidemiology, and translational studies (e.g., immunology, immunogenetics, pharmacogenetics, and drug resistance)—both within the network, and with external collaborators. In RePORT-South Africa, the focus is on biomarker studies that will improve our understanding of TB pathogenesis, diagnosis, and treatment response.

As part of TB RiCC 3.0, Vanderbilt investigators will co-lead the RePORT International Scientific Review Committee (Dr. Timothy Sterling), and the Data Harmonization Working Group (Dr. Stephany Duda). The REDCap data collection software used by RePORT International was developed at Vanderbilt, and the team will collaborate on the implementation of REDCap forms and the implementation of REDCap extensions in support of TB RiCC 3.0. Vanderbilt will work closely with Rutgers and Frontier Science in TB RiCC 3.0 to review, monitor, and provide data quality assurance review of the data from RePORT networks. In addition, these entities will collaboratively provide performance metrics from country network protocols, as well as oversee and guide the expansion of specimen inventory integration with REDCap clinical data to allow investigators easier access and understanding of the data and biological specimens available for further scientific use across the RePORT Consortium. The Vanderbilt team will also help administer pilot funding to sites to develop capacity and expertise in clinical trials, including TB preventive therapy and vaccines.

Frontier Science Foundation

Frontier Science Foundation is a non-profit research foundation that provides state-of-the-art data management and statistical capabilities and collaborates with sponsors, universities, and publicly funded research networks to perform infectious disease research. Various NIH-funded networks use Frontier Science as their data management center. In this role Frontier Science provides laboratory information management software, dedicated central databases, virtual specimen repositories, data visualization and dashboard tools, data collection instrument design and implementation, data quality assurance and control, customized reports, and training and support resources.

Frontier Science's efforts for TB RICC 3.0 will be led by Sue Siminski, President and CEO of Frontier Science and project PI, who has extensive data management experience, including serving as the Data Center PI or MPI on numerous NIH funded projects, and has led Frontier Science's efforts in several harmonization projects. In addition, Dr. Soyeon Kim, a statistician who has been working in the area of HIV and TB research for more than 20 years, will lead a team of statisticians from Frontier who offer statistical expertise to TB RiCC 3.0. Alex Benns, Frontier Science Project Manager, coordinates the multi-disciplinary team.

As an essential component of the TB RICC 3.0 Data Hub, Frontier Science will work closely with country-level data centers, Rutgers, and Vanderbilt in support of various efforts on this project. Frontier Science will support data harmonization efforts and provide guidance on form creation within REDCap for the collection of common data elements. Frontier Science will also implement a data QA process to provide high-level quality control. This data QA process will use a vetted set of operating procedures and workflows founded on a mature quality management system, under the guidance of data and process QA experts. Frontier Science will assist with the preparation and retention, in a centralized database, of datasets that contain approved harmonized core variables and will use these data to build portal dashboards for data

visualization/monitoring and cross-network study progress. In addition, Frontier Science will support site data management training efforts at RePORT network data centers to ensure consistent data handling and best practices, including good clinical practice as it relates to participant privacy.

IGM-Fiocruz/RePORT Brazil (FIOTEC)

Institute Gonçalo Moniz/Fiocruz, located in Salvador, Bahia, is a prominent institution that forms part of RePORT-Brazil and shares in the leadership of the TB RICC 3.0. Dr. Bruno Andrade, an accomplished infectious diseases physician-scientist and co-PI of RICC, is the Principal Investigator of the national consortium since 2019, closely collaborating with Vanderbilt University Medical Center and other partner institutions. RePORT-Brazil has significantly contributed to the understanding of tuberculosis (TB) determinants in the Brazilian population, and globally, helping other RePORT networks in India, Philippines, South Africa, and Indonesia.

FIOCRUZ analytical team contributes significantly to TB RICC 3.0 Data Harmonization Working Group and the Genetic and Molecular Epidemiology protocol. In addition, the team provides valuable support and guidance to investigators throughout the RePORT networks in data analysis and visualization. As experts in data handling and interpretation, FIOCRUZ plays a critical role in helping researchers extract meaningful insights from complex datasets. Dedicated teams provide bioinformatic expertise specializing in systems biology, who analyze and integrate multiplatform data, including proteomics and transcriptomics. Institute Gonçalo Moniz/Fiocruz houses the Clinical and Translational Research Institute (CTRI), a state-of-the-art Luminex facility, equipped with an advanced Luminex xMAP INTELLIFLEX System, can simultaneously detect and quantify over 500 protein molecules, such as cytokines and hormones. It plays a vital role in accelerating collaboration between RePORT networks and is an essential component of the RICC biomarker protocol in collaboration with Rutgers University.

Johns Hopkins University

Johns Hopkins University (JHU) in Baltimore, USA, will be instrumental in directing the TB RiCC 3.0 Capacity Building activities SWG to support research capacity building across all RePORT networks. Led by Dr. Amita Gupta, Professor of Infectious Diseases and Chief of the Division of Infectious Diseases, and Dr. Robert Bollinger (Capacity Building SWG, Training).

JHU will seek to implement two strategic capacity strengthening activities. 1) Development of six enduring e-learning courses designed to support strategic RiCC research priorities that will be available to all RiCC investigators and staff. Two courses will be developed in each of years 1-3; and 2) Establishment of an intensive, highly selective, faculty-mentored Scholars Program for six early-stage investigators, who will commit for a two-year period. This program will provide selected candidates two years of training support and 1:1 mentorship from an experienced faculty mentor in the RePORT networks.

JHU will also provide a communications/public relations professional to support development of a portfolio of materials which will be available to the RePORT Consortium to engage potential new partners and promote awareness to their respective governments and sponsors.

Junior Investigator Abstracts: Presentations

POPULATION PHARMACOKINETICS OF MOXIFLOXACIN IN INDIAN PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS.

Junior Investigator: **Prerna R. Arora** (**RePORT India)**
RePORT Investigators: Tester F. Ashavaid, Jeffrey A. Tornheim.
RePORT Team: JR Resendiz-Galvan, RV Lokhande, A Gupta, ZF Udwadia, L Pinto, P Denti, the MUKT Study Team and the lndo-SA Study team.

Background and rationale: Multidrug-resistant tuberculosis (MDR-TB) incidences are increasing globally with India being the highest burden country of MDR-TB (27%). Moxifloxacin, a fluroquinolone, is a WHO recommended Group A drug for MDR-TB treatment and is included in both shorter 4-month regimens for drug- susceptible tuberculosis, and in some 6-month regimens for MDR-TB. Higher doses overcome low- level drug resistance, but can increase the risk of toxicity. There is limited literature about the pharmacokinetics of MFX in an Indian population.

Methods: We analyzed data from the RePORT India Parent Protocol MDR-TB MUKT at Hinduja Hospital, Mumbai, India. Participants were adolescents and adults enrolled within 7 days of treatment initiation. Participants receiving either 400mg daily, 400mg twice-daily, 600mg daily or 800mg daily dosing regimens. Intensive pharmacokinetic collections were performed at O (pre-dose), 1, 2, 4, 6 and 8 hours post-dose at months 1, 2 or 4 after treatment initiation, while the sparse sampling was performed at O and 2 hours post-dose at months 2, 6 and 12. Drug levels were performed on liquid chromatography mass spectrometry and the pharmacokinetic analysis was performed in nonlinear mixed-effect model software (NONMEM v7.4) software. Different structural models (one- and two- compartments) were tested to describe the pharmacokinetics of the drugs. Between occasion variability was implemented for the absorption parameters. Monte-Carlo simulations were performed using the final model to estimate the probability of target attainment using a literature-derived f AUCo_24/MIC ratio target of>53, which is equivalent to a total f AUCo-24/MIC ratio of>106.

Results: This analysis included data from 178 participants of whom 116 (65%) were female with a median age of 26 years (interquartile range, IQR 20-35yrs), weight 55kg (IQR 47-66kg), and a median fat-free mass of 39kg (IQR 33-47kg). Data analyzed included a total of 1403 moxifloxacin concentrations, of which 276 represented intensive sampling and 1127 sparse sampling. The pharmacokinetics of moxifloxacin was best described by a two-compartment model with first-order elimination and first order absorption with series of transit compartments. The typical values for clearance, intercompartmental clearance, central and peripheral volume were 16.5 L/h, 0.593 L/h, 91.1 L, and 98.4L, respectively. Simulations showed that a moxifloxacin dose of 800mg once daily is adequate to reach target efficacy with a probability of >90% if MIC is 0.5 mg/L. However, for a MIC of 0.25 mg/L a dose of 400mg daily is enough to achieve the target in >90% of simulated individuals. Interestingly, we found the model to be significantly affected by drug-drug interactions with an observed interaction when moxifloxacin was co-administered with para-amino salicylic acid.

Conclusion: We developed the population pharmacokinetics model for moxifloxacin for Indian population which is in accordance with literature reports. We have observed a probability of target attainment of>90% at 400mg daily dose if the MIC is <0.25 and at 800mg daily dose if MIC is 0.5. Along with other covariates, drug-drug interactions play vital role in pharmacokinetics and can significantly affect the drug efficacy and safety in patients.

IMPACT OF PREMORBID NUTRITIONAL STATUS ON TUBERCULOSIS SEVERITY IN INDIA: A MULTICENTER PROSPECTIVE COHORT ANALYSIS

Junior Investigator: **Xinyi Du (RePORT India)**
RePORT Investigator: Chinnaiyan Ponnuraja
RePORT Team: N Gupte, S Sarkar, A Gupta, DJ Christopher, H Kornfeld, V Viswanathan, JJ Ellner, CR Horsburgh, Jr., C Padmapriyadarsini, P Sinha

Background and rationale: India bears a quarter of the global tuberculosis (TB) burden. Previous studies have indicated that more than 50% of persons with TB in India are undernourished and undernutrition is associated with increased risk of unfavorable TB outcomes and mortality. In this study, we assessed the impact of undernutrition prior to TB onset on markers of TB severity.

Methods: We analyzed prospectively collected data for persons with TB aged ≥18 years from five Regional Prospective Observational Research for Tuberculosis (RePORT) – India sites. Using weight loss due to TB disease reported by participants alongside height and weight at treatment initiation, we were able to calculate body mass index (BMI) prior to TB onset (premorbid BMI) for participants. We built univariate and multivariable regression models to assess relationships between premorbid BMI and markers of disease severity. We used logistic regression for lung cavitation and high-grade sputum smear positivity (defined as smear grade ≥2+), and linear regression for percentage of lung affected and time to positivity of Mycobacteria Growth Indicator Tube (MGIT; weeks). The models included age, sex, symptom duration a priori, and variables with p<0.2 in univariate analysis.

Results: Of the 1587 participants for whom we could calculate premorbid BMI, a total of 226 (14.24%) participants were undernourished prior to disease onset. After adjusting for age, sex, symptom duration, income, HIV status, diabetes, smoking, and alcohol misuse (defined as having an AUDIT-C score ≥3 for females and ≥4 for males), moderate-severe undernutrition (BMI<17kg/m^2) prior to disease onset was associated with increased odds of lung cavitation (adjusted odds ratio [aOR] 1.79, 95% confidence interval [CI]: 1.14, 2.86), increased odds of high bacillary sputum grade (aOR 1.05, 95%CI: 0.75, 1.48), an average 4.66% (95%CI: 0.85, 8.47) more lung affected, and an average 0.31 (95%CI: -0.61, -0.0064) shorter time to liquid culture positivity.

Conclusion: Our findings indicate that moderate-severe undernutrition prior to TB disease onset is associated with more severe disease which may explain the association between undernutrition and unfavorable treatment outcomes. The use of premorbid BMI strengthens this analysis since it addresses confounding from the bidirectional relationship between TB

disease severity and undernutrition. Our study provides a rationale for population-scale interventions in regions with high TB rates to reduce undernutrition.

Table 1. Multivariable models of the effect of premorbid body mass index (BMI) on cavitation, percentage of lung affected, sputum smear positivity, and mycobacterial burden, India

	Cavitation		Lung affected (%)		Sputum smear positivity		MGIT (TTP) (weeks)	
	aOR[1] (95%CI)	p	Adjusted relative percentage[2] (95%CI)	p	aOR[3] (95%CI)	p	Adjusted relative time to positivity[4] (95%CI)	p
Premorbid BMI								
<17 kg/m^2	1.79 (1.14, 2.86)	0.014	4.66 (0.85, 8.47)	0.017	1.05 (0.75, 1.48)	0.75	-0.31 (-0.61, -0.0064)	0.045
>=17 kg/m^2	Ref		Ref		Ref		Ref	

1. The adjusted odds ratio (aOR) is adjusted for age, sex, symptom duration, income, HIV, diabetes, smoking, and alcohol misuse
2. The adjusted relative percentage is adjusted for age, sex, symptom duration, income, diabetes, smoking, and alcohol misuse
3. The adjusted odds ratio (aOR) is adjusted for age, sex, symptom duration, income, HIV, and smoking
4. The adjusted relative time to positivity is adjusted for age, sex, symptom duration, income, HIV, diabetes, and smoking

THE SOUND OF SILENT RNA: THE ROLE OF LONG NON-CODING RNA ON TUBERCULOSIS IN FOUR DIFFERENT POPULATIONS

Junior Investigator: **Artur Trancoso Lopo de Queiroz (RePORT Brazil)**
RePORT Investigator: Bruno Bezerril de Andrade
RePORT Team: ER Fukutani, CL Vinhaes, TF Mota, M Araújo-Pereira, AN Gupte, NP Kumar, Arriaga MB, Sterling TR, Babu S, Gaikwad S, Karyakarte R, V Mave, V Kulkarni, N Gupte, M Paradkar, V Viswanathan, H Kornfeld, A Gupta

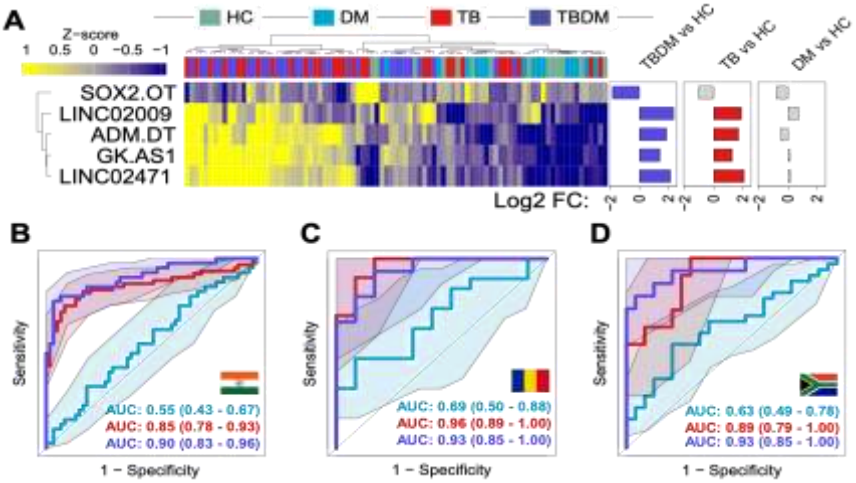
Background and rationale: Tuberculosis (TB) is one of the leading causes of death worldwide, and diabetes mellitus (DM) is one of the major co-morbidities associated with TB. DM influences TB disease, affecting the TB-associated chronic inflammatory response, increasing the risk of developing active TB and impairing the TB treatment response. We recently described a strong influence of population-specific differences on TB and TB/DM gene expression in four different countries. Herein, we evaluated the dynamics of long non-coding RNA (lncRNA) expression and its association with TB and DM.

Methods: Gene expression data from TB, DM, TB/DM, and healthy controls (HC) from Brazil, India, Romania and South Africa were obtained, comprising a total of 429 samples from two different cohorts, RePORT and TANDEM. The non-coding RNA gene(ncRNAs) expression was retrieved and differential expression analysis was performed on Brazilian data, comparing both TB and TB/DM with HC. All ncRNAs (lncRNAs and MicroRNAs) differentially expressed were used as input to a dimensionality reduction algorithm, to select the most informative variables and the accuracy of the selected variables was validated in samples from India, Romania, and South Africa. To identify the potential pathways regulated by those lncRNAs, a correlation analysis between the most informative lncRNAs and all genes was performed. The most correlated genes were used in enrichment analysis.

Results: We identified a total of 103 differentially expressed ncRNAs in the TB and TB/DM differential expression comparison, comparing with HC. From these, 5 lncRNAs were identified as most informative in the dimensionality reduction approach: ADM-DT, LINC02009, LINC02471, SOX2-OT and GK-AS1. ADM- DT was downregulated in TB/DM compared to HC, while the other four lncRNAs were upregulated in TB and TB/DM compared to HC. The validation analysis showed that the 5 model-select lncRNAs presented a moderate accuracy classifying DM from HC samples, with an AUC of 0.652 (C.I. 0.44~0.86). However, they had substantial accuracy when discriminating TB from HC with an AUC of 0.91 (C.I. 0.82~0.99) and discriminating TB/DM from HC with an AUC of 0.98 (C.I. 0.95~1.00), in all other 3 countries. The correlation analysis to identify the potentially associated genes identified similar pathways in Brazil and India for both TB and TB/DM conditions. The identified pathways were related to interleukin and interferon signaling, Toll- like receptor cascades, neutrophil degranulation, and infection-associated pathway.
Conclusion: Despite the lack of information regarding their biological function, the 5 most informative lncRNAs were strongly correlated with genes associated with pathways related to the immune response regulation against TB. The pattern of expression of lncRNAs was observed in the 4 different country populations and associated with TB. This suggests that the 5 model-selected lncRNAs play an important role in the regulation of genes associated with the TB immune response. This regulation is observed independent of the glycemic status (TB

only or TB/DM) and higher variation of population-associated gene expression.

Figure 1. Result of classification analysis from lncRNAs: A - Heatmap of Model-selected lncRNAs expression data from Brazilian samples. The right annotation are the bar plot displaying the log2 fold change each comparison. ROC curves displaying the lncRNA biomarker's overall classification performance of each condition compared with HC in the different studied sites: In B are the subjects from India, in C subjects from Romania and D subjects from South Africa.



GENE SIGNATURES FOR MONITORING TREATMENT RESPONSE AND PREDICTING CURE AMONG TB PATIENTS IN BRAZIL

Junior Investigator: **Simon C Mendelsohn (RePORT South Africa)**
RePORT Investigators: Mark Hatherill, Thomas Scriba, Bruno Andrade, and Timothy Sterling
RePORT Team: SC Mendelsohn, SK Mbandi, ATL Queiroz, A Penn-Nicholson, MC Figueiredo, VC Rolla, M Cordeiro-Santos, AL Kritski,

Background and rationale: The global TB treatment success rate was estimated at 86% for new and relapse TB cases in 2021 (WHO Global TB Report). The WHO still recommends sputum smear microscopy or culture at the end of the intensive phase of treatment for monitoring response to TB treatment in adults, however these are poor predictors of treatment failure and other adverse outcomes. There are currently no non-sputum biomarkers in clinical practice for monitoring response to TB treatment and predicting cure or treatment failure. Host-blood gene signatures are an attractive option which could be implementable at the point-of-care.

Methods: We measured six concise gene signatures (Francisco2, Maertzdorf4, Penn-Nicholson6 [RISK6], Suliman4 [RISK4], Sweeney3, and Thompson5 [RESPONSE5]) by microfluidic multiplex real-time qPCR on whole blood RNA samples collected from 48 drug-sensitive pulmonary TB patients at the start, month 2, and after completion of 6 months of standard TB treatment, and 99 healthy close contacts (77 QFT– and 22 QFT+), recruited in the RePORT-Brazil cohort. All TB patients were successfully treated (cured), and did not have recurrence through 2 years of follow-up. Score distributions were compared between timepoints and groups using Wilcoxon Signed-Rank and Rank-Sum tests, respectively, and receiver operating characteristic area under the curve (AUC).

Results: RISK6 signature scores were lower through month 2 ($p=0.0031$) and completion ($p<0.0001$) of treatment compared to baseline. Accordingly, RISK6 was able to differentiate TB patients prior to the start of treatment from those who had received 2 months (AUC 0.68, 95%CI 0.57-0.79) or 6 months (AUC 0.89, 95%CI 0.81-0.95) of treatment. RISK6 scores in TB patients who had completed 6 months of treatment were not different from those of healthy close contacts (AUC 0.55, 95%CI 0.45-0.65; $p=0.41$). The RESPONSE5 signature, specifically designed to capture response to TB treatment and predict cure, was able to differentiate successful treatment response by month 2 of treatment ($p<0.0001$; AUC 0.76, 95%CI 0.66-0.85). The other parsimonious signatures were similarly able to track response to TB treatment and predict cure, and scores among individuals who had successfully completed treatment were similar to those of healthy controls.

Conclusion: In this pilot cohort, where every TB patient had clinical cure by six months, RISK6 and the other concise gene signatures tracked the response to TB treatment, with scores returning to healthy control levels by the end of treatment. It follows that the parsimonious signatures could potentially be used to monitor response to TB treatment and determine both successful and unsuccessful clearance of Mtb. The next step is to test host-response gene signature performance for differentiating successful treatment from treatment failure and recurrence. Biomarkers which could predict treatment failure and recurrence early in the course of treatment would be useful for clinical care (to adjust TB treatment) and clinical trial design (to reduce sample size).

INCIDENCE AND DETERMINANTS OF SUBCLINICAL AND CLINICAL RECURRENCE OF TUBERCULOSIS AMONG CURED PULMONARY TUBERCULOSIS PATIENTS IN INDIA

Junior Investigator: Mandar Paradkar (RePORT India)
RePORT Investigators: Vidya Mave, Nikhil Gupte, Amita Gupta
RePORT Team: S Gaikwad, C Padmapriyadarsini, M Naik, S Raskar, K Thiruvengadam, A Gupte, M. Barthwal, K Sonya, J Golub

Background and rationale: Subclinical pulmonary tuberculosis (PTB), defined as viable detectable mycobacterium TB (Mtb) in absence of symptoms, has emerged as a potential contributor to continued TB transmission, impeding global efforts for ending TB. The infectiousness and transmission potential of sub-clinical TB came to light in national population-based surveys and household contact investigations where Mtb bacilli was detected in sputum among asymptomatic individuals. However, data are limited in high-burden settings. Using two large prospective cohorts, we assessed the incidence and determinants of subclinical and clinical TB-recurrence in India.

Methods: Individuals with PTB were recruited to two observational cohorts namely, "The Cohort for TB Research by the Indo-US Medical Partnership (CTRIUMPh)" and "Impact of Diabetes on TB Treatment Outcomes (TBDM)", established between 2013 and 2019 in Pune, and Chennai, India. Drug sensitive PTB participants ≥14 yrs of age who successfully completed anti-TB treatment (ATT) (clinical response with or without microbiological evidence of cure at the end of ATT) and followed for up to 18-months post-ATT completion were included in the analysis. They underwent mycobacteriology testing (smear microscopy and cultures) at 6, 12, and 18-months post-ATT and suspected TB-recurrence visit. TB-recurrence was categorized as subclinical (asymptomatic, positive mycobacteriology (smear and/or culture)), and clinical recurrence (TB symptoms of any duration, with or without positive mycobacteriology, and clinical decision to treat). We calculated incidence of TB-recurrence and performed Cox-regression to identify its determinants. Sensitivity analysis was performed in a subset with culture-confirmed cure.

Results: Of 1196 PTB cases enrolled, 888 (74%) aged ≥14 years successfully completed ATT while the remaining either failed treatment, died, or were lost to follow-up. These 888 included, 561 (63%) males, 407 (46%) > 35 years of age, 484 (55%) undernourished, 277 (31%) diabetics, 23 (3%) HIV infected, 159 (18%) reported smoking, 251 (29%) consumed smokeless tobacco, 270 (30%) consumed alcohol, 726 (82%) received thrice weekly regimen, while 552 (62%) received extended duration of treatment. Sixty-six (8%) had TB-recurrence (overall incidence rate of 7.7 (95% CI: 6.0 – 9.8) / 100 PY). Of these, 38 (58%) had clinical and 28 (42%) had subclinical TB, with an incidence rate of 4.5 (IQR:3.2-6.2), per 100-PY and 3.3 (IQR:2.2-4.8), respectively. Median time to clinical and subclinical TB-recurrence

was 5.4 (IQR:3.6–8.4) and 6.9 (IQR:4.9–9.3) months post ATT-completion, respectively. In the model adjusted for age, gender, BMI, and smokeless tobacco; age-group 14–35 years (aHR–3.0, 95% CI– 1.2–7.2, p=0.02) and smokeless tobacco (aHR–2.3, 95% CI– 1.0–5.1, p=0.05) were the independent risk factors for subclinical TB-recurrence (Table 1); while the age group >35 years (aHR–2.5, 95% CI– 1.3–5.0, p=0.02) and undernutrition (aHR–2.4, 95% CI– 1.1–5.1, p=0.02) were independent risk factors for clinical TB-recurrence after adjusting for age, gender, BMI, smokeless tobacco, alcohol consumption and pretreatment AFB smear. The results of sensitivity analysis (n=755 with culture-confirmed TB cure) were consistent with those from all participants with successful ATT completion (n=888).

Conclusion: Subclinical TB-recurrence was as common as clinical TB-recurrence among persons with cured TB in India. Our findings highlight the importance of strategies to identify and treat subclinical TB.

Table 1: Risk factors for subclinical tuberculosis recurrence among successfully treated adult pulmonary tuberculosis cases.

Risk factor	N	Subclinical TB recurrence, n (%)	Unadjusted Hazard Ratio uHR (95% CI), (p value)	Adjusted H Ratio aHR (95% CI), (p)
Gender				
Male	531	20 (3.8)	Ref	Ref
Female	319	8 (2.5)	0.7 (0.3 – 1.5) (0.34)	0.7 (0.3 – 1.8) (0.49)
Age				
> 35	383	7 (1.8)	2.5 (1.1 – 5.0.) (0.03)	3.0 (1.2 – 7.2) (0.02)
14 - 35	467	21 (4.5)	Ref	Ref
Body mass index				
Normal	334	7 (2.1)	Ref	Ref
Obese	58	1 (1.7)	0.8 (0.1 – 6.6) (0.84)	1.3 (0.2 – 10.5) (0.84)
Underweight	456	20 (4.4)	2.1 (0.9 – 5.0) (0.09)	2.0 (1.0 – 5.1) (0.05)
HIV infection				
No	805	28 (3.5)	-	-
Yes	20	0 (0)		
Diabetes mellitus				
No	582	21 (3.6)	Ref	
Yes	268	7 (2.6)	0.8 (0.3 – 1.8) (0.53)	-
Smoking				
No	629	24 (3.8)	Ref	-
Yes	151	4 (2.6)	0.7 (0.2 – 2) (0.48)	
Tobacco chewing				
No	586	15 (2.6)	Ref	Ref
Yes	235	13 (5.6)	2.3 (1.1 – 4.8) (0.03)	2.3 (1.0 – 5.1) (0.05)
Alcohol consumption				
No	565	18 (3.2)	Ref	
Yes	254	10 (3.9)	1.1 (0.5 – 2.4) (0.81)	-
CXR Cavity				
No	387	7 (1.8%)	Ref	-
Yes	271	11 (4.1%)	2.2 (0.8 – 5.6) [0.11]	

CXR Ralph Score > 0				
No	56	1 (1.8%)	Ref	-
Yes	579	15 (2.6%)	1.4 (0.2 – 10.8) [0.73]	
Treatment Regimen				
Thrice Weekly	693	23 (3.3)	1 (0.4 – 2.6) (0.97)	-
Daily	152	5 (3.2)	Ref	
Treatment Duration				
Extended	530	16 (3.0)	1.6 (0.5 – 4.7) (0.42)	
Not Extended	209	4 (1.9)	Ref	-
Baseline AFB Smear				
Negative	271	6 (2.2)	Ref	
Positive	577	22 (3.8)	1.7 (0.7 – 4.3) (0.23)	-
Month 2 AFB Smear				
Negative	636	19 (3.0)	Ref	
Positive	49	2 (4.1)	1.3 (0.3 – 5.4) (0.76)	-

A COMPREHENSIVE MULTIOMIC ANALYSIS OF THE TUBERCULOSIS AND DIABETES INTERACTION

Junior Investigator: Mariana Araújo Pereira (RePORT-Brazil)

RePORT Investigator: Bruno Bezerril de Andrade
RePORT Team: CL Vinhaes, ER Fukutani, GC Santana , MB Arriaga , BB Duarte, AMS Andrade, MC Figueiredo, VC Rolla, AL Kristki, MC Santos, TR Sterling , ATL Queiroz

Background and rationale: Tuberculosis (TB) continues to be one of the leading causes of death worldwide. Understanding the immune response to TB and its association with other conditions, such as diabetes (DM), is crucial for improving anti-TB treatment (ATT) outcomes. By leveraging innovative multi-omic technologies, our study was designed to uncover novel insights into the physiological changes induced by TB with or without DM comorbidity.

Methods: We conducted an analysis using samples from 76 participants from RePORT-Brazil at multiple time points, including baseline, 2 months, and 6 months after initiating ATT. These patients were grouped according to TB and DM status, in four distinct clinical groups: only TB, only DM, TBDM, and a control group of non-TB/non- DM. We employed a machine learning algorithm to analyze data, combining cytokine and chemokine levels and gene expression data from peripheral blood, as well as urinary eicosanoids. Through rigorous cross-validation, we identified several markers that helped to discriminate between the different groups.

Results: In this study, we identified a distinct multi-omic expression profile at baseline that identified TB cases regardless of the DM status. TB participants had higher baseline Leukotriene E(LTE)-4, 11-dehydrothromboxane (dTx)B2, Prostaglandin D Metabolite (PGDM), F-Box Protein (FBXO)6, SECTM1 and LINCO2009 levels, as well lower Matrix Metalloproteinase (MMP)-28 in contrast with non-TB participants. Moreover, we observed a positive correlation between the levels of SECTM11 and FBOX6 mRNA and the mycobacterial load in TBDM, as indicated by the acid-fast bacilli (AFB) grade.

Conclusion: Our study presents evidence for the potential of multi-omic markers to improve the diagnosis, treatment, and understanding of TB pathogenesis and its interactions with comorbidities such DM. By integrating technologies and applying advanced data analysis techniques, we have taken a significant step towards understanding TB immunopathology, that can enhance clinical care, and ATT outcomes in the field of TB research.

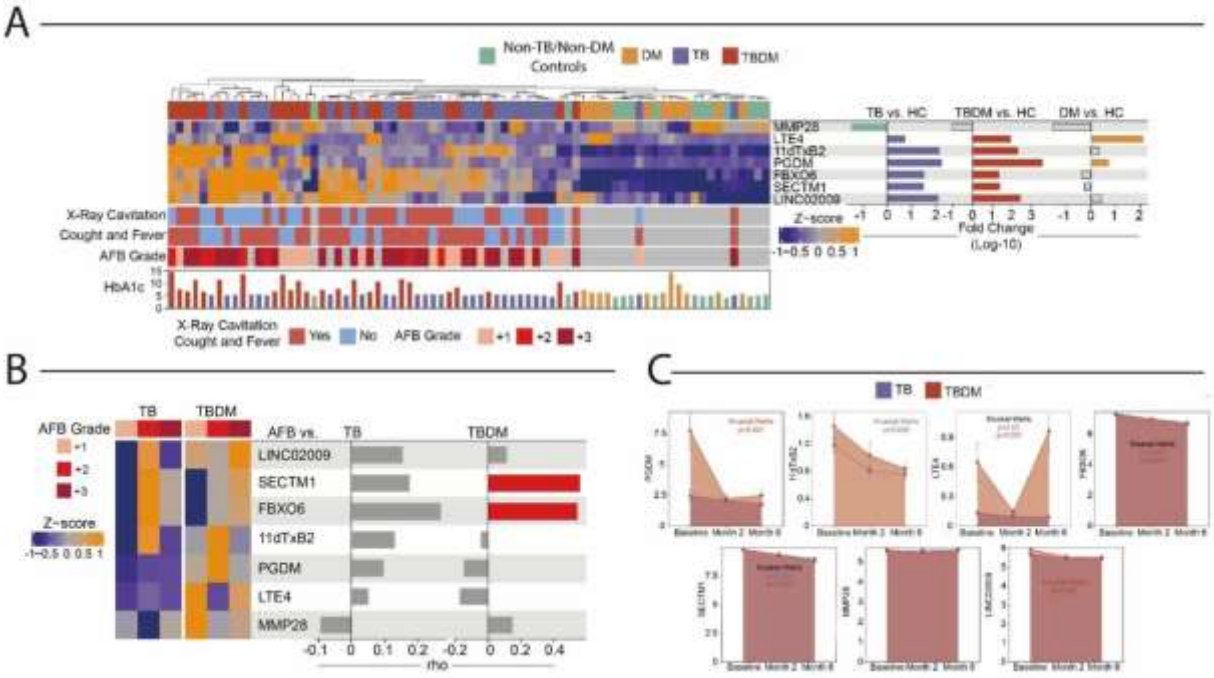


Figure 01. Distinct multiomics expression profiles can identify Tuberculosis Infection Regardless the Glycemic Status. Right panel. (A) A hierarchical cluster analysis (Ward method with 100 × bootstrap) was employed to test the overall expression of plasma cytokines, gene expression and urinary eicosanoids in the study population. Dendrograms represent Canberra distance. Left panel. Differential expression analysis was used to calculate the fold-changes and show differences in biomarkers levels for each clinical group (TB, TBDM and DM) versus control. Differences that reached statistical significance after adjustment for multiple comparisons (adjusted p-value< 0.05) are represented in colored bars. (B) Left panel. A hierarchical cluster analysis (Ward method with 100 × bootstrap) was employed to evaluate the multiomic markers expression according to the AFB grade in TB and TBDM, as indicated. Right panel. A Spearman correlation analysis was used to study the influence of the AFB grade in the multiomic markers expression. The rho values were showed. Red bars indicate correlation with p-value<0.05. (C) A Box plot was used to test the changes in the multiomic levels in months 2 and 6 after ATT.

Junior Investigator Abstracts: Posters

EFFECT OF SMOKING ON LONGITUDINAL INTERFERON-ϒ RELEASE ASSAY RESULTS AMONG CLOSE CONTACTS OF PEOPLE WITH PULMONARY TUBERCULOSIS

Junior Investigator: **María B. Arriaga (RePORT Brazil)**
RePORT Investigator: Timothy R. Sterling
RePORT Team: G Amorim, MC Figueiredo, C Staats, AL Mritski, M Cordeiro-Santos, VC Rolla, BB Andrade
Other authors: AMS Andrade, MS Rocha, V Nascimento, JM Cubillos-Angulo, J Rebouças-Silva, SM. Viana, P Brito, SRN Santos, A Ramos, AG Costa, J Silva, JG de Oliveira , A Benjamin, A Gomes-Silva, FM Sant'Anna, FP Ignácio, MC Lourenço, EC Silva, ASR Moreira, Mello, M Turner
Background and rationale: Diagnosis of *M. tuberculosis* (Mtb) infection in close tuberculosis (TB) contacts is critical for TB control. Interferon-gamma release assays (IGRAs) diagnose Mtb infection, but the test is limited by assay variability, including the conversion (negative to positive) and reversion (positive to negative) of IGRA responses that may not always reflect changes in Mtb infection status. Several studies have revealed that smoking is a risk factor for Mtb infection and TB disease but its effect on longitudinal IGRA results remains unknown.

Methods: We conducted a multi-site prospective study in RePORT-Brazil between 2015-2019 among close contacts of adults with culture- confirmed pulmonary TB. IGRA testing was performed at baseline, month 6 and month 24-30 after enrollment. IGRA results were categorized as IGRA-positive (maintained from baseline to last visit), IGRA-conversion (from negative to positive at any time), IGRA- reversion (from positive to negative at any time), and IGRA-negative (maintained from baseline to last visit). Associations between IGRA results and smoking status at baseline (current/former vs never) in contacts were evaluated using propensity score-adjusted logistic regression models to avoid overfitting. More specifically, we first estimated the propensity of smoking using Lasso. Next, this estimated propensity score was used as a covariate in the main outcome model, which regressed the outcome (IGRA-positive, IGRA-conversion, IGRA-reversion) on smoking status.

Results: There were 430 close contacts of 139 TB cases. Of the contacts, 89 (21%) were IGRA-positive, 30 (7%) were converters, and 30 (7%) were reverters; 22 (5.1%) had an indeterminate result. The frequency of smoking among contacts was 26 (29.2%), 7 (23.3%) and 3 (10%) in IGRA- positive, IGRA-conversion and IGRA-reversion groups, correspondingly. Smoking in contacts was associated with lower odds for IGRA-reversion (adjusted odds ratio=0.09; 95% confidence interval=[0.01;0.73]). We did not detect associations between smoking and IGRA-positive or IGRA-conversion at the 5% level.
Conclusion: Contacts who reported smoking (past/former) had lower odds of reverting from an IGRA-positive to an IGRA-negative result. Our findings highlight the importance of smoking on longitudinal IGRA results. This has implications for clinical care and clinical trials in which IGRA status is monitored or used as an outcome, such as TB vaccine trials.

Table 1. Logistic regressions were used to test associations between "smoking" among close contacts of pulmonary TB cases and reversion, conversion, and positive IGRA results in TB close contacts.

Model 1: IGRA-positive (n=89) vs. IGRA-negative (n=259)		
Smoking (contact)*	1.14 (0.53-2.45)	0.741
Propensity score [1]	1.90 (0.60-6.03)	0.279
Model 2: IGRA-conversion (n=30) vs. IGRA-negative (n=259)		
Smoking (contact)*	1.87 (0.57-6.16)	0.305
Propensity score [2]	0.28 (0.04-2.17)	0.223
Model 3: IGRA-reversion (n=30) vs. IGRA-positive (n=89)		
Smoking (contact)*	0.09 (0.01-0.73)	0.024
Propensity score [3]	6.34 (0.62-64.52)	0.118

Table note:
*For "smoking (current/former)" was used as reference "never-smoking".
Lasso regression was used for selecting variables that were included in Propensity Score for "smoking".

1 Variables used in the propensity score model: alcohol comsumption, BCG, passive smoking, sex, and age (in contacts) + cavities in X-ray (in TB cases).

2 Variables used in the propensity score model: alcohol comsumption, BCG, sex, and age (in contacts) + cavities in X-ray (in TB cases).

3 Variables used in the propensity score model: alcohol comsumption, sex, BCG, passive smoking, illicit drug use, and age (in contacts) +sex, alcohol use, passive smoking, illicit drug use and age (in TB cases).

Abbreviations: IGRA: Interferon-ϒ Release Assay, TB: tuberculosis, CI: confidence interval.

DIVERSE IMMUNE MARKERS OF RISK AND PROTECTION IN CHILDREN AND ADULT HHCS OF TB PATIENTS.

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RePORT Investigators: VL Valluri, R Vankayalapati
Other Authors: VSK Neela, D Tripathi, AK Bogam, V Mallidi, S Joshi

Background and rationale: Children are at a higher risk of TB infection and disease progression because of their immature immune system. Childhood and adolescent tuberculosis constitute approximately 20–40% in high-TB burden countries. Household contacts (HHCs) of TB patients are at high risk of developing latent or active TB disease because of their exposure to index case. Identifying HHCs who are likely to develop active TB is important to control TB. By following HHCs every 6 months and performing transcriptional and metabolomic studies, we could determine whether development of active TB disease is preceded by specific changes in immune cell profile. The majority of studies investigating novel TB biomarkers focus on adults and it is unlikely the same biomarkers can be accurately extrapolated to paediatric populations given the considerable differences in immune responses to Mtb between adults and children. Our studies on TB biomarkers in children address these research gaps while having potential as triage tests, distinguishing between those who are likely to develop TB and need prophylactic treatment.

Methods: Children (2-18 years) and adults (>18 years) were recruited and followed for 2 years to determine changes in immune signatures of conversion into latent and active TB progression. At every study visit PBMCs were isolated and flow cytometry was performed to phenotype various immune cell populations (NK, monocytes and T-cell subsets) in fresh PBMCs. Remaining PBMC were cultured with ESAT-6 and CFP-10 to quantify RNA expression and measure cytokines in culture supernatants. Plasma from converters (n = 5) and nonconverters (n = 5) at baseline (0 months) and during follow-up (24 months) was analyzed by liquid chromatography– mass spectrometry (LC-MS) to identify metabolomic signatures in children and adults.

Results and conclusion: We observed that the immune cell phenotypes in children and adults are different and distinct, with children having significantly higher CD4+ T cell subsets whereas CD8+ T cells are higher in young adults. NK cell subsets however are lower in children, increase with age. Metabolites associated with LTBI conversion in children were Betaine, Proline, Lyso-PC, Glycochenodeoxycholate, whereas those in adults were Docosahexaenoate, Homocysteine. These markers can be used to predict high risk individuals for LTBI conversion and TB progression. Experiments to elucidate the role of these metabolites on immune response to Mtb and the mechanistic studies are underway. This study was supported by DBT-CRDF and NIH as a part of RePORT India consortium.

ASSESSMENT OF TB SEVERITY AND ITS' EFFECT ON TREATMENT OUTCOMES AMONG PEOPLE WITH TBDM CO-MORBIDITY: STUDY FROM SOUTH INDIA

Junior Investigator: Mythili Dhanasekaran (RePORT India)
RePORT Investigators and Team: A Devarajan, S Kumpatla, V Viswanathan, H Kornfeld

Background and rationale: Diabetes Mellitus (DM) affects the tuberculosis (TB) disease presentation by clinical, bacteriological, radiological aspects and also outcomes of TB treatment and vice versa. Studies shows that DM increases three times the risk of TB and also increases the unfavourable TB treatment outcomes such as failure, death and recurrence. The aim of this study was to explore the severity of TB disease among people with TBDM co-morbidity and its' effect on TB treatment outcomes.

Methods: A total of 446 newly diagnosed Pulmonary TB patients enrolled in EDOTS (Effects of Diabetes on Tuberculosis Severity) study conducted during 2014 to 2018 in TB units in North Chennai, South India. The participants were categorised into KnownDM(KDM, n=179), New-DM(NDM, n =105), Normoglycemic(NG, n=162). After exclusion of culture negative, not willing, moved out of area, totally 340(KDM-144, NDM=80&NG=116) participants were considered for analysis. 3+ smear grade, 3+ culture grade, cavitation at baseline, > 2 zones of lung involvement in chest x-ray were categorized as advanced TB. 1+ and 2+ smear&/1+ and 2+ culture grades, absence of cavitation, <2 zones of lung involvement in chest x-ray as minimal disease.
Results: The median (min, max) lung affected percentage score in KDM group was 24(0.0, 90.0), NDM 26(0.0, 80.0), NG 18(0.0, 90.0) at baseline. The difference between NDM and NG was statistically significant(p=0.031). Lower lobe of lung involvement is significantly higher in KDM (36.4%) and NDM (35.0%) compared to NG (18.3%);P<0.01. In people with culture 3+, the rate of unfavourable outcome was 10.3% in KDM, significantly differ from NG (28.3%); p=0.018, while difference was not statistically significant with NDM (25.8%); p=0.056. In people with advanced TB, the rate of unfavourable outcome was high in NDM (22.2%) and NG (21.1%) compared to 9.5% KDM (P<0.05).

Conclusion: Lung involvement and also the rate of unfavourable outcome was higher among people with TB and new DM co-morbidity compared to normoglycaemic.

RETREATMENT AFTER LOSS TO FOLLOW-UP AND ANTI-TUBERCULOSIS THERAPY OUTCOMES IN BRAZIL BETWEEN 2014 AND 2021: A NATIONWIDE STUDY OF DISEASE REGISTRY DATA.

Junior Investigator: **Beatriz Barreto Duarte (RePORT Brazil)**
RePORT Investigators: BB Andrade, TR Sterling
RePORT Team and Other Authors: K Villalva-Serra, JP. Miguez-Pinto, M Araújo-Pereira, VMS Campos, G Rosier, BMF Nogueira, ATL Queiroz, VC Rolla,, M Cordeiro-Santos, AL Kritski,, PF. Rebeiro, MM Rodrigues

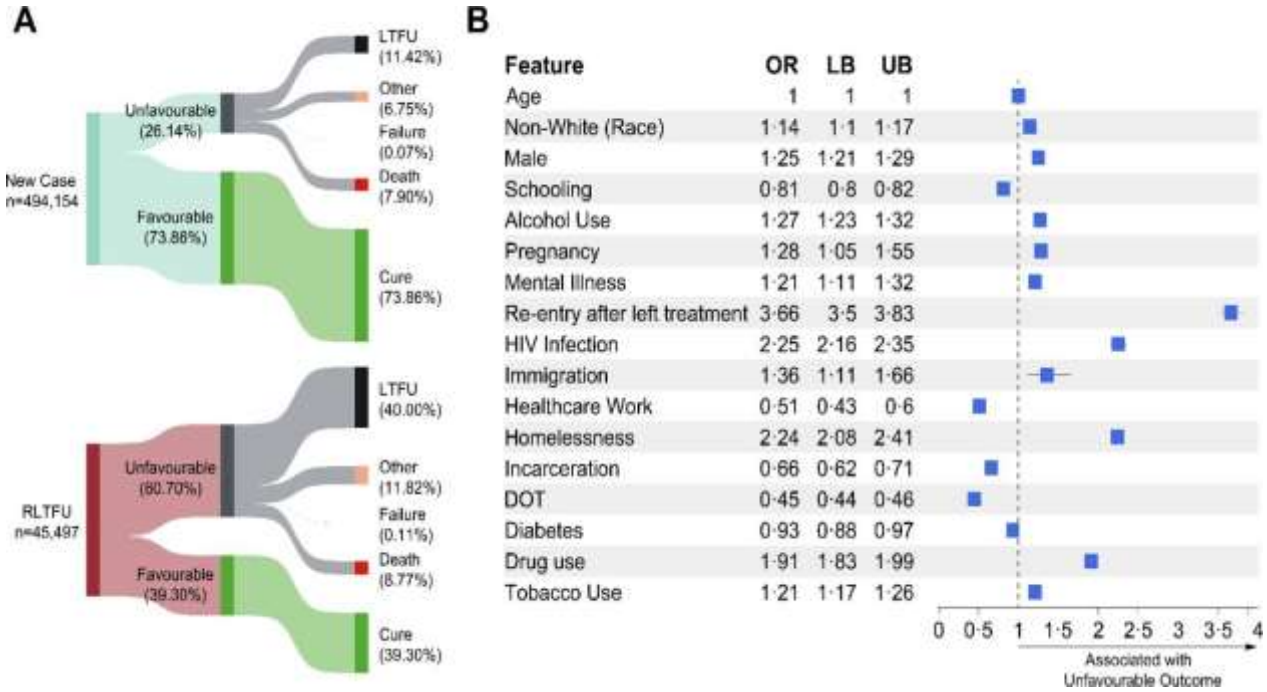
Background and rationale: Adherence to anti-tuberculosis treatment (ATT) in Brazil remains a challenge in achieving the goals set forth by the World Health Organization (WHO). Patients who are lost to follow-up (LTFU) during treatment pose a significant public health problem, and often receive inadequate attention from the healthcare system when they return for retreatment. Furthermore, there is a lack of knowledge about the factors associated with ATT outcomes in this patient group. This study aims to investigate the clinical and epidemiological factors associated with unfavorable ATT outcomes in retreatment cases after LTFU (RLTFU) in Brazil.

Methods: We conducted an observational study of tuberculosis cases >18 years-old reported to the Brazilian National Notifiable Disease Information System between 2014 and 2021. Only cases with information about the outcome were included in the analyses. Clinical and epidemiologic variables were compared between the study groups (new tuberculosis cases and RLTFU). Next, we applied a multinomial regression model to identify variables associated with increased risk of any unfavorable outcome (death, failure, or LTFU) or of each individual ATT outcome.

Results: Of 718,583 reported cases of tuberculosis, 540,101 were eligible for inclusion in the study, consisting of 494,154 new tuberculosis cases and 45,947 RLTFU. Tuberculosis case notification was unevenly distributed among the country's states in both groups with higher numbers reported from Southeastern Brazil. Unfavorable ATT was higher among RLTFU than new TB cases (60.7% vs 26.1%).RLTFU was a significant risk factor for any unfavorable ATT independent of other features such as homelessness, pregnancy, and healthcare work, immigration, and incarceration. Furthermore, RLTFU was the main risk factor for LTFU; living with HIV was the top risk factor for death. Also, we evaluated the risk factors for unfavorable outcome in just the RLTFU group; the risk factors were similar to the overall study population (Figure).

Conclusion: RLTFU was a substantial factor driving increased risk of unfavorable tuberculosis outcomes, especially a new LTFU. The rates of treatment success in the RLTFU group were far short of the WHO End Tuberculosis Strategy targets throughout Brazil. By shedding light on the impact of prior LTFU on ATT outcomes, this study provides valuable insights for healthcare providers, policymakers, and other stakeholders working to improve treatment adherence and tuberculosis control in Brazil.

Figure: (A) Sankey diagrams show frequencies of each tuberculosis treatment outcome in the SINAN registry of TB cases identified between 2014 and 2021 among New Cases and TB cases reported among RLTFU (retreatment after loss to follow-up), and (B) results from binomial regression model quantifying the associations between various risk factors for unfavorable treatment outcomes in the overall population of the study.



CONSISTENCY AND VARIABILITY IN LONGITUDINAL INTERFERON GAMMA ASSAY IN PREGNANT AND POSTPARTUM WOMEN IN PUNE, INDIA.

Junior Investigator: **Aditi Pramod Kole (RePORT India)**
RePORT Investigators: A Gupta
RePORT Team and Other Authors: S Naik, R Bhosale, V Kulkarni, P Deshpande, J Mathad, M Alexander

Background and rationale: Immune changes of pregnancy increase the risk of TB progression from latent to active TB. The interferon gamma release assay (IGRA) is a latent TB diagnostic. In non-pregnant studies, people with conversion and reversion of IGRA results had a higher TB incidence. But data in pregnant and postpartum women is sparse. This study examines consistency and variability of IGRA in pregnant and postpartum women with and without HIV in India.

Methods: Pregnant women with and without HIV were enrolled between June 2016 and December 2019, in an observational prospective cohort study, Pregnancy Associated Changes In Tuberculosis Immunology (PRACHITi) in Pune, India. IGRA was done during pregnancy and repeated at delivery and 6 months postpartum (QuantiFERON-TB Gold In-Tube until Sep 2017; after that, QuantiFERON-TB Gold Plus). In this variability analysis, 192 women who had IGRA results at all three timepoints are included. Conversion was defined as a positive result (TB antigen- nil > 0.35) following a negative result. Reversion was defined as negative or indeterminate result at later from a baseline positive status at pregnancy. We compared proportion of conversions and reversions from pregnancy to postpartum between women with/without HIV using chi square test.

Results: We enrolled 234 pregnant women, mostly from low socio-economic strata, at a median of 21 weeks gestation (IQR:17.3 – 26.5). Women with HIV had a median CD4 count of 476 cells/mm^3 (IQR:399 – 586); all were on antiretroviral therapy. In our study, overall reversion rate at delivery was 42/135 (31%) and at postpartum was 7/135 (5.2%) from IGRA+ status at pregnancy. Conversion rate from IGRA- status at pregnancy was 1/57(5.8%). Among 30 IGRA+ women with HIV, 15 (50%) remained positive, 13 (43%) reverted at delivery 2 (7%) remained negative and 11 (31%) converted at postpartum. Among 105 IGRA+ women without HIV, 73 (69%) remained positive, 29 (28%) reverted at delivery and 5 (5%) remained negative, 20 (19%) converted at postpartum. Significantly higher proportion of IGRA+ women with HIV reverted at delivery (p=0.04) and reverted at delivery but converted at postpartum(p=0.04). Among the 36 IGRA- women with HIV, 31 (89%) remained negative, 1 (3%) converted at delivery. Among the 21 IGRA- women without HIV, 16 (76%) remained negative, one (5%) converted at delivery and remained negative at postpartum. There was no significant conversions IGRA- women in our study. Of the 117 IGRA+ (21 with HIV and 96 without HIV) at antepartum and delivery, 7 (5.9) (4 with HIV (19%) and 3 (3.1%) without HIV developed active TB during postpartum (p<0.01).

Conclusion: In our study consistent IGRA+ at pregnancy and delivery and not IGRA conversion and reversion progressed to active TB infection postpartum especially those with HIV. Overall variability is higher in women with HIV compared to without, indicating lower interferon-gamma (IFN-γ) response in HIV infection as reported in the literature. Larger longitudinal studies in pregnant women with IGRA testing at various time points would help in confirming the further significance of these findings.

PARTICIPANT CHARACTERISTICS AND UNFAVORABLE OUTCOMES IN BRAZIL AND INDIA: A REPORT INTERNATIONAL DATA HARMONIZATION STUDY

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RePORT Investigators and Other Authors: G Amorim, Nikhil Gupte, AGupte, M Paradkar, M Naik, S Gaikwad, MMS Rodriques, ATL Queiroz, M Figueiredo, V Mave, VC Rolla, A Kritski, M Cordeiro-Santos, S Sarkar, S P Babu, V Vishwanathan, H Kornfeld, P Priyadarshini, EH Luke, SV Bala, YS Kumar, B Thangakunam, DJ Christopher, P Salgame, CR Horsburgh, J Ellner, A Gupta, TR Sterling, BB Andrade, M Robinson

Background and Rationale: A significant proportion of persons with drug-sensitive pulmonary tuberculosis (TB) experience an unfavorable treatment outcome (treatment failure, TB recurrence, death, or lost to follow-up) despite receipt of effective antituberculosis therapy (ATT). Predicting an individual's clinical outcome, based on routinely collected longitudinal clinical and laboratory data, throughout receipt of ATT and in the months following ATT completion could inform clinical care during follow-up and improve outcomes. Despite the potential value of a prediction model, few multi-national datasets comprising harmonized information on individuals from diverse epidemiologic and geographic backgrounds exist.

Methods: We leveraged data from participants enrolled in the Regional Prospective Observational Research for Tuberculosis (RePORT) Brazil and India cohort from 2014-2019. Individuals with drug-sensitive pulmonary TB were initiated on standard ATT. We formed a multinational team of researchers from RePORT Brazil and India to strategize on harmonization of entry visit data. We focused on variables collected that were most likely to be important in development of a prediction model, based on cross-cohort availability, expert opinion, and prior published literature. For this initial harmonization only the first unfavorable outcome was considered. We censored those who did not have an outcome recorded.

Results: Among 1998 cross-consortium harmonized participants, 281 (14%) experienced an unfavorable outcome by 12 months, including death, failure, lost to follow-up, and recurrence (Table 1, Figure 1). We successfully created a baseline dataset that included information on sociodemographic, clinical, laboratory, and microbiological data (Table 1). While similar by age and sex, significant differences in the make-up of the cohorts by comorbidities (diabetes, HIV), sociodemographic factors (substance use), and BMI are apparent. Brazil had a higher primary study outcome of death (5.1%), compared to the Indian cohorts, where death often followed failure or recurrence. Recurrence was more common in the Indian cohorts (2.5-5.9%) compared to Brazil (0.9%).

Conclusion: We successfully completed initial harmonization of the RePORT India and Brazil datasets. This harmonization highlights inherent differences between the cohorts. It also sheds light on the complexities of trying to merge data between protocols that while similar, have inherent differences (such as the collection of recurrence outcomes, ascertainment of death). Future directions include harmonization of additional variables and longitudinal data, incorporation of RePORT India Parent Protocols as well as potentially RePORT South Africa. Additional work is underway using this robust data to generate prediction models of adverse TB treatment outcomes.

Table 1. Baseline characteristics and outcomes of RePORT Brazil, RePORT India Common Protocol, and CTRIUMPh.

Characteristic (Baseline)	All N=1998	RePORT Brazil N=1056	RePORT India Common Protocol N=521	CTRIUMPh N=421	p-value
Age	37.0 (25.0-48.0)	36.0 (25.0-49.0)	39.0 (26.0-48.0)	36.0 (24.0-49.0)	0.1
Male Sex	1330 (66.6%)	700 (66.3%)	358 (68.7%)	272 (64.6%)	0.4
Body Mass Index (IQR)	19.1 (16.8-21.7)	20.2 (18.3-22.5)	18.0 (16.0-20.6)	17.4 (15.6-19.8)	<0.001
Diabetes	562 (28.3%)	264 (25.2%)	177 (34.4%)	121 (28.7%)	0.001
HIV	241 (12.4%)	221 (21.1%)	6 (1.2%)	14 (3.3%)	<0.001
Ever Smoker	860 (44.1%)	552 (52.3%)	174 (33.4%)	134 (36.0%)	<0.001
Ever Alcohol	1309 (66.6%)	888 (84.1%)	237 (45.5%)	184 (47.3%)	<0.001
Baseline Hemoglobin g/dL (IQR)	12.0 (10.5-13.3)	12.1 (10.7-13.3)	12.0 (10.4-13.5)	11.7 (10.3-13.0)	0.05
CXR Cavitation (Yes)	1065 (55.4%)	522 (49.8%)	359 (72.4%)	184 (48.8%)	<0.001
Smear Results					<0.001
1+	554 (27.8%)	265 (25.1%)	145 (28.2%)	144 (34.2%)	
2+	510 (25.6%)	250 (23.7%)	146 (28.3%)	114 (27.1%)	
3+	378 (19.0%)	249 (23.6%)	87 (16.9%)	42 (10.0%)	
Negative	396 (19.9%)	203 (19.2%)	115 (22.3%)	78 (18.5%)	
Positive (grade unknown)	64 (3.2%)	0 (0.0%)	22 (4.3%)	42 (10.0%)	
Scanty	90 (4.5%)	89 (8.4%)	0 (0.0%)	1 (0.2%	
Outcome by Month 12					
Death	63 (3.2%)	41 (3.9%)	12 (2.3%)	10 (2.4%)	
Failure	93 (4.7%)	26 (2.5%)	18 (3.5%)	49 (11.6%)	
Lost to Follow up (6-12 months)	100 (5.0%)	72 (6.8%)	28 (5.4%)	0 (0.0%)	
Lost to Follow up (0-6 months)	104 (5.2%)	56 (5.3%)	26 (5.0%)	22 (5.2%)	
Recurrence	21 (1.1%)	5 (0.5%)	8 (1.5%)	8 (1.9%)	
Tx Complete	1617 (80.9%)	856 (81.1%)	429 (82.3%)	332 (78.9%)	
End of Study Outcome					
Cure	1354 (68.0%)	638 (60.9%)	402 (77.2%)	314 (74.6%)	
Death	76 (3.8%)	53 (5.1%)	13 (2.5%)	10 (2.4%)	
Failure	105 (5.3%)	30 (2.9%)	25 (4.8%)	50 (11.9%)	
Lost to Follow up	408 (20.5%)	318 (30.3%)	68 (13.1%)	22 (5.2%)	
Recurrence	47 (2.4%)	9 (0.9%)	13 (2.5%)	25 (5.9%)	

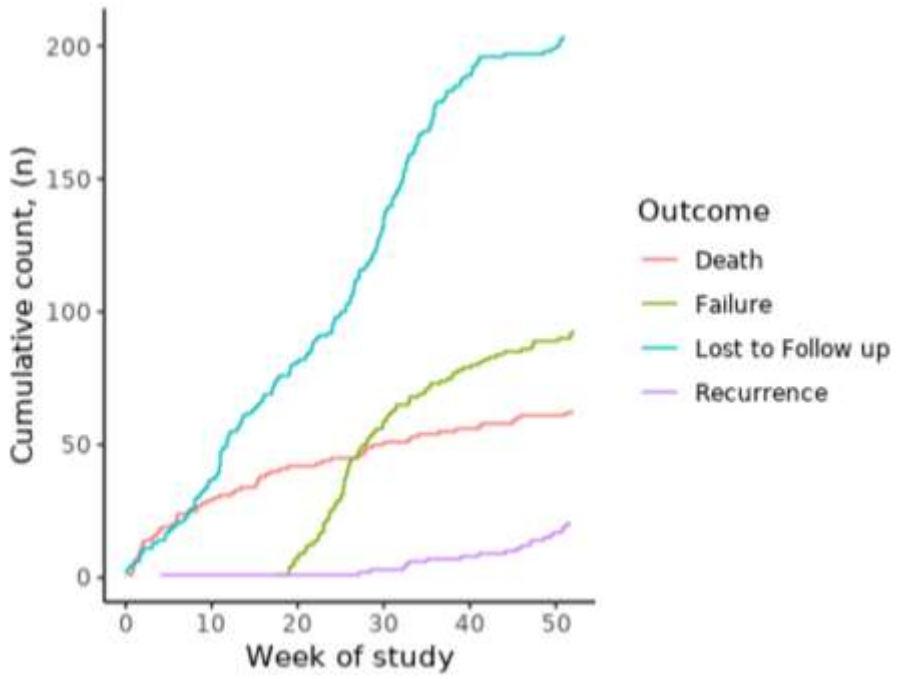

Figure 1. Cumulative count of unfavorable outcomes in the first 12 months for all participants in RePORT Brazil, RePORT India Common Protocol, and CTRIUMPh.

MEMORY LIKE NK CELLS AS BIOMARKERS TO PREDICT TREATMENT RELAPSE IN ACTIVE TB PATIENTS.

Junior Investigator: **Neela Venkata Sanjeev Kumar (RePORT India)**
RePORT Investigators: VL Valluri, R Vankayalapati
RePORT Team and Other Authors: KP Devalraju, D Tripathi, AK Bogam, V Mallidi, MS Ansari, S Joshi

Background and rationale: Tuberculosis (TB) remains a social and public health threat in almost all developing countries. Identification of the risk factors, tailored to reflect local disease epidemiology in high-burden countries, is key to controlling the global TB epidemic. We have previously shown that Mtb modulates host immune responses during infection by affecting cell phenotypes. However, it remains unclear how these mechanisms are regulated and what impact they have on immunometabolism during TB disease which could lead to a relapse. The lack of reliable biomarkers of TB reoccurrence and treatment response has hindered TB management and drug development. Well defined correlates of TB relapse at baseline facilitates improved TB treatment regimen thereby effective utilization of resources. Therefore, we aimed to explore the implications of changes in immune cells, specifically NK cell responses, in the evolution of TB relapse.

Methods: Patients with sputum smear positive for AFB or chest X-ray confirmed pulmonary tuberculosis / EPTB were recruited and followed for 1-year post treatment. PBMCs were isolated and flow cytometry was used to identify various immune cell populations (NK, monocytes and T-cell subsets) in fresh PBMCs. Remaining PBMC were cultured with ESAT-6 and CFP-10 to quantify RNA expression and measure cytokines in supernatants. Patients who were declared cured or treatment completed but report of signs and symptoms with a positive sputum smear were categorized as TB relapse.

Results: CD3-CD56+CD27+CCR7+ memory like NK cell percentages were significantly high in patients who developed TB relapse compared to those who did not. No significant differences in CD4+, CD16+, CD14+CD16+, CD16+CD56+, or CD4+CD25+FoxP3+ cells were observed. Serum hormones, cytokine responses and RNA sequencing will be determined to understand the effect of these markers in TB recurrence.

Conclusion: These findings lay the groundwork for the development of novel markers in addition to memory-like NK cells for development TB relapse at baseline. This study was supported by NIH, USA (Grant ref no: R01AI123310-04).

ASSESSMENT OF LATENT TB INFECTION IN HOUSEHOLD CONTACTS OF ACTIVE PULMONARY DRUG RESISTANT TB PATIENTS

Junior Investigator: **Heeral U.B. Pandya (RePORT India)**
RePORT Investigators: Tester F. Ashavaid and Camilla Rodrigues
RePORT Team and Other Authors: Priti Dubey, Manasi Kudtarkar, PR Arora, U Surve, ZF Udwadia, J Mullerpattan, L Pinto, A Sunawala, A Gupta, JA. Tornheim

Background/Rationale: Tuberculosis (TB) is the leading cause of death caused by *M. tuberculosis* (M.tb) across the world. Latent TB Infection (LTBI), an asymptomatic condition, is a state of persistent immune response stimulated by M.tb antigens with no clinical evidence of active TB. Household contacts of patients diagnosed with TB are at a higher risk of contracting the disease. Along with tuberculin skin test (TST), QuantiFERON TB gold plus (QFT-Plus) is being widely used for the detection of LTBI. It is an in-vitro laboratory test to measure responses to TB-specific peptide antigens in the blood and is a type of Interferon Gamma release assay (IGRA). The present study aims to evaluate the proportion of LTBI in household contacts (HHCs) of Active (drug resistant) DR-TB patients.

Methods: A total of 62 HHCs of active pulmonary DR- TB patients were enrolled in the RePORT India Parent Protocol - MDR-TB MUKT study. HHCs were defined as participants who lived in the same dwelling as of the MDR patients during 3 months prior to the diagnosis of MDR-TB with at least 8 hours of exposure/day with the index case. TST, QFT-Plus assay, and other diagnostic tests were performed at baseline and prospective follo w-ups at months 4-6, 12, 18 and 24.

Results: Out of the 62 participants, 32 (51.6%) were females with majority of the participants from 41-50 years age group. In this study, 24 (39%) participants had positive results at baseline for both TST and QFT while for QFT-Plus and the TST individually there were 37 (59.7%) and 32 (51.6%), respectively. Only about 8 (13%) of the participants were negative for both TST and QFT till the end of their follow-up. About 58% of participants who were positive by both TST and QFT at baseline were household contacts of pre-XDR index case. Out of the 30 participants with negative TST at baseline, 13 (43%) turned positive at by Month 6 and 4 (13%) at Month 12. Similarly, the participants who were negative for QFT at baseline (n=25 including 1 indeterminate), 8 (31%) participants' QFT status converted to positive by Month 6, 3 (11.5%) at Month 12, 1 (3.8%) at Month 18 of follow up. Only one participant had TST and QFT conversion at the same time point (Month 12) but no active TB symptoms. Culture was carried out for 50 participants who were able to produce sputum at baseline, all of which were negative. Surprisingly, we also observed 1 participant who showed negative TST, QGIT and culture result who developed active TB disease at 7th month of follow-up. None of the patients had any active TB symptoms.

Conclusion: The results showed that more than half of the participants were positive for latent TB from their initial visit to 12 months of follow-up. Hence, household contact investigation and monitoring is an effective tool to check for latent TB and its progression to active TB.

ISONIAZID MONORESISTANCE AND ANTI-TUBERCULOSIS TREATMENT OUTCOME IN PERSONS WITH PULMONARY TUBERCULOSIS IN BRAZIL

Junior Investigator: Mariana Araújo Pereira (RePORT Brazil)
RePORT Investigator: Bruno Bezerril de Andrade
RePORT Team and Other Authors: MB Arriaga, ACC Carvalho, R Spener-Gomes, FM Sant'anna, BMF Nogueira, MC Figueiredo, MM Turner, M Cordeiro- Santos, VC Rolla, TR Sterling, AL Kritski

Background and rationale: Tuberculosis (TB) remains a serious public health problem. The high burden of drug- resistant TB (DR-TB) makes it difficult to achieve the goals of the End of TB Strategy by 2035, proposed by the World Health Organization (WHO). In 2020, there were 1.4 million incident cases of isoniazid resistance in the world, of which 1.1 million were isoniazid monoresistant (Hr). However, there are few data published among patients with Hr-TB in high burden countries, and the effect of Hr on anti-TB treatment (ATT) outcome.

Methods: We collected baseline clinical and demographic characteristics, as well as ATT outcome in persons with pulmonary TB (PWPTB) enrolled in the RePORT-Brazil cohort between June 2015-June 2019 (follow-up through June 2021) in three Brazilian regions; and among all PTB cases reported to the National Notifiable Disease Information System (SINAN) in the same period and inclusion criteria. In both cohorts, patients were grouped and compared according to drug-susceptibility testing (DST) results. Only those with Hr or isoniazid-sensitive result remained in the analysis. Binomial logistic regression models were employed to evaluate whether Hr was independently associated with unfavorable ATT outcome: death, failure, or recurrence, compared to cure.

Results: Among 1,020 PWPTB enrolled in RePORT-Brazil and 60,804 TB cases identified in SINAN, 688 (67.5%) and 21,197 (34.9%) cases were included in the study, respectively. In RePORT-Brazil, 4.2% had Hr and the frequency of unfavorable ATT outcome was not significantly different between groups with or without Hr (20.7% vs 11.9%, respectively; p=0.23). In SINAN, 1.4% presented with Hr and the frequency of unfavorable outcomes was significantly higher in those with Hr in contrast to patients with isoniazid-sensitive TB (9.1% vs 3.05%, p<0.001). Using a binomial logistic regression model to adjust for potential confounders, Hr was associated with unfavorable outcomes (OR: 3.34 [95%CI: 2.06-5.40], p<0.001) in the SINAN cohort, independent of other clinical characteristics.

Conclusion: Hr detected prior to ATT was predictive of unfavorable outcomes. Our data reinforce the need for high TB burden countries to prioritize DST and detect Hr early in the course of ATT. Effective treatment regimens for TB that is Hr are needed to improve outcomes.

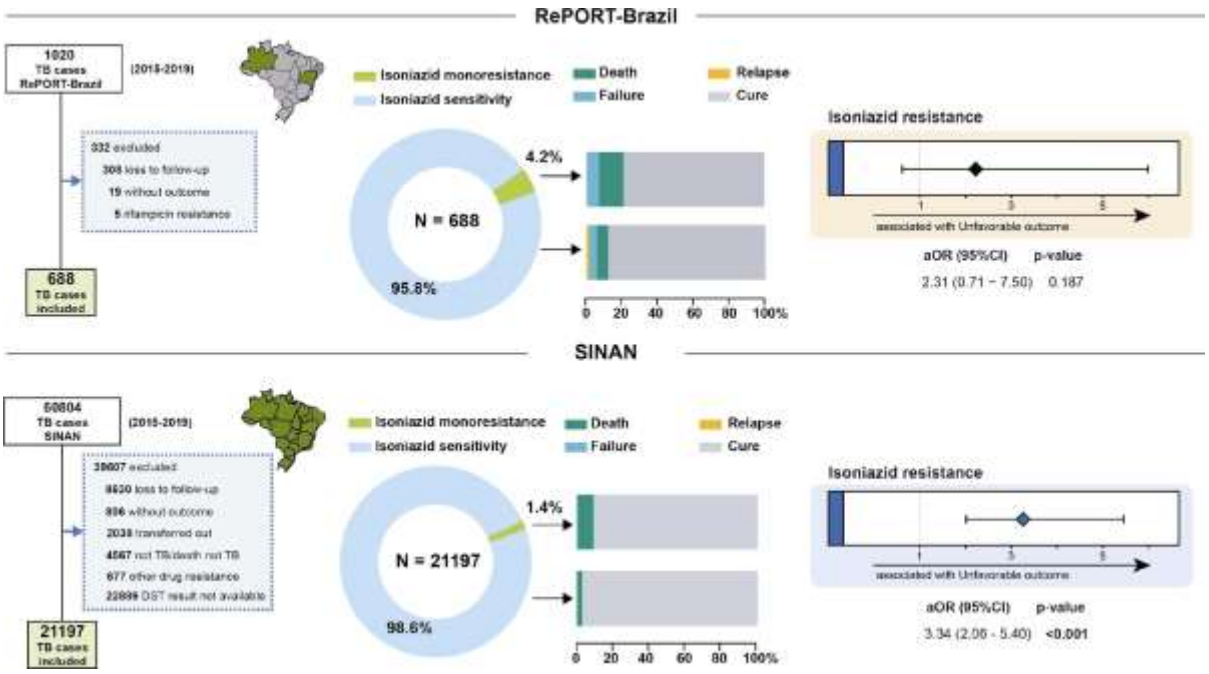

Figure 01. Top: Study flow chart of participants enrolled in RePORT-Brazil sites, between 2015 and 2019, of which 688 cases were included. A binomial logistic regression analysis was employed using sex, age, race, direct observed therapy, clinical form, HIV, alcohol consumption, tobacco use, drug use, diabetes and resistance to isoniazid. Bottom: Study flow chart of TB cases reported in SINAN database, with 21,197 cases included in the study. A binomial logistic regression analysis was employed using the same variables of the model with. P- values described in bold-type font were statistically significant. The treatment outcomes analysis of each group revealed that TB patients with isoniazid monoresistance experienced increased occurrence of unfavorable treatment outcomes. Abbreviations: [aOR] – adjusted Odds Ratio; [CI] – confidence interval.

PHARMACOKINETIC ANALYSIS OF CYCLOSERINE CONCENTRATIONS IN AN INDIAN POPULATION WITH MULTI- DRUG RESISTANT TUBERCULOSIS.

Junior Investigator: **Juan Eduardo Resendiz-Galvan (RePORT India and RePORT South Africa)**
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Background and rationale: According to WHO guidelines, cycloserine is a part of the MDR-TB regimen and is frequently used as part of longer treatments in India. Cycloserine inhibits alanine racemase and D-alanine ligase, the two essential enzymes for cell wall synthesis in Mycobacterium tuberculosis. Overdose of cycloserine increases the probability of neuropsychiatric concentration-dependent toxicity. It is minimally metabolized by the liver, and approximately 60 to 70% is reported to be excreted by the kidneys. We aim to describe the pharmacokinetics of cycloserine in an Indian population.

Methods: Patients with MDR-TB were enrolled in a prospective observational study at the P. D. Hinduja National Hospital in Mumbai, India. Study participants received MDR-TB treatment as per national guidelines, including weight-adjusted cycloserine dose of 250 mg 2-3 times daily. Blood was drawn before and at 1, 2, 4, 6, and 8 h after an observed dose, during the 1st or 2nd month of treatment. Creatinine clearance was estimated using the Cockcroft-Gault equation as an indicator of renal function. The pharmacokinetic analysis was performed in nonlinear mixed-effect model software version 7.4. Cycloserine was quantified by a validated liquid chromatography mass spectrometry assay. Concentrations below the lower limit of quantification (0.78 mg/L) were not censored by the laboratory and were incorporated in the analysis.

Results: Data were available from 50 Indian participants contributing 300 observations and only 1 value was below the lower limit of quantification. The participants were 66% female, and their median weight, fat-free mass, age, and creatinine clearance were 54 (interquartile range (IQR): 46-64) kg, 39 (IQR: 32-46) kg, 26 (IQR: 21-32) years, and 108 (IQR: 94.4-134) mL/min, respectively. Most participants (n=47, 94%) received 250 mg of cycloserine 3 times daily, for a total daily dose of 750 mg. Treatment also included clofazimine (84% of participants), bedaquiline (46%), pyrazinamide (40%), ethambutol (30%), para-aminosalicylic acid (24%), ethionamide (20%), and kanamycin (6%). A one-compartment model with first-order elimination and transit compartment absorption best described the pharmacokinetics of cycloserine. Allometry using fat-free mass improved the estimation of disposition parameters. The best model included the assessment of two different elimination pathways, renal and non-renal. The model estimated a typical value for clearance and volume of 1.6 L/h and 35 L, respectively. Renal elimination was estimated using the creatinine clearance and accounted for 60% of the typical value for clearance.

Conclusion: A one-compartment model described the pharmacokinetics of cycloserine in an Indian population. There are only a few models in the literature; one includes a mixed population (United States, Georgia, and Bangladesh) dosed with cycloserine and total clearance reported at 2.0 L/h, a second one in South African population but dosed with terizidone (2 cycloserine molecules) and reporting a clearance of 0.51 L/h for this drug. A third model, also from South Africa, reported a renal elimination for cycloserine of 0.43 L/h, which is lower than the value founded in the present study, and the overall exposure in this cohort of Indian participants is lower. This highlights the relevance of studying further the differences between populations, comedication, etc.

RePORT International Network
Data Tables: Phase 1 (as of July 28th, 2023)

Table 1	Cohort A - TB Index Cases	
	Date Enrollment Completed (yyyy-mm-dd)	Sample Size Enrolled (n)
RePORT Brazil	2015-06-01	1188
RePORT China	2021-05-14	198
RePORT India	2017-04-05	724
RePORT Indonesia	2017-02-13	490
RePORT Philippines (UPM)	2022-11-22	581
Philippines - DLSMHI (MDR-TB)	2022-04-04	159
RePORT South Africa	2016-12-20	962
TOTAL		4302

Table 2	Cohort A - TB Index Cases - Enrollment Demographics					
	Total Enrolled (n)	Adult Males (n, %)*	Adult Females (n, %)*	Adults Median Age (yrs)	Children <18 years of age (n)	Participants with HIV (n)
RePORT Brazil	1188	785 (66%)	403 (34%)	36	3	255
RePORT China	198	139 (70%)	59 (30%)	NA	0	0
RePORT India	724	499 (70%)	214 (30%)	40	10	11
RePORT Indonesia	490	303 (62%)	187 (38%)	41	0	31
RePORT Philippines (UPM)	581	361 (62%)	220 (38%)	44	79	7
Philippines - DLSMHI (MDR-TB	159	103 (66%)	52 (34%)	43	4	2
RePORT South Africa	962	206 (58%)	147 (42%)	36	610	393
TOTAL	4302	2396 (65%)	1282 (35%)		706	699

*Some sites may have included children under 18 years of age.

Table 3	Cohort A - TB Index Cases - Protocol Visits				
	Baseline (n)	Month 1 (n)	Month 2 (n)	End of Tx or (Month 6) (n)	Post TX Follow-up (12 months+) (n)
RePORT Brazil	1188	658	1012	822	752 (CALL 1; M12) 668 (CALL 2; M18) 647 (CALL 3; M24)
RePORT China	198	168	141	104	92
RePORT India	724	662	612	516	516
RePORT Indonesia	490	362	333	263	0
RePORT Philippines (UPM)	581	497	458	226	M6 PTX -158 M24 PTX- 102
Philippines - DLSMHI (MDR-TB)**	159	150	146	128	93
RePORT South Africa	962	701	661	303	354
TOTAL	4302	3198	3363	2362	1965*

*Includes M6 for UPM

**End of Tx for DR-TB is longer: 82 (Month 9), 46 (Month 18)

Table 4 Cohort A - TB Index Cases - Outcomes

	RePORT Brazil (n)	RePORT China (n)	RePORT India (n)	RePORT Indonesia (n)	RePORT Philippines (UPM) (n)	RePORT Philippines (DeLaSalle) MDR Cases (n)	RePORT South Africa (n)	TOTAL (n)
Bacteriologic Cure	346	178	517	233	134	113	85	1606
Bacteriologic Status Indeterminate	251	0	14	17	223	15	159	679
Bacteriologic Failure	32	0	22	9	4	2	11	80
Bacteriologic Relapse	3	0	10	0	2	-	2	17
Not Tuberculosis	NA	0	12	20	-	1	82	115
Death (if not bacteriologic/clinical outcomes)	59	4	14	64	19	9	32	201
Treatment Incomplete	75	0	28	0	16	-	8	127
Loss to Follow-up	220	16	88	58	6	5	232	625
Not Evaluated	0	0	0	89	-	-	0	89
Other	48	0	0	0	83	8	242	381
Moved out of Area	7	0	0	0	10	7	0	24
MTB Negative	104	0	0	0		56	92	252
Ineligible	7	0	0	0	55	0	17	79
Total	1152	198	705	490	552	216	962	4275

Table 5 Cohort A - TB Index Cases Biorepository & Aliquots Per Site

		Whole Blood (EDTA) - DNA	Whole Blood (Heparin) - PBMC	Whole Blood (Heparin) - Plasma	Whloe Blood (QFT+)	Whole Blood - PAXgene RNA	Urine	Saliva	Sputum	MTB Isolate
RePORT Brazil	Baseline	4276	2551	11615	NA	1059	11731	NA	4363	4060
	M1	NA	NA	6170	NA	NA	NA	NA	1982	649
	M2	NA	2065	9643	NA	908	9980	NA	2714	150
	EOT/M6	NA	1630	7872	NA	704	8013	NA	1267	3
RePORT China	Baseline	792	0	792	0	792	792	0	792	436
	M1	676	0	66	0	664	664	0	664	84
	M2	544	0	544	0	544	544	0	544	8
	EOT/M6	388	0	388	0	388	388	0	388	0
RePORT India	Baseline	2731	1486	5875	0	720	2889	1645	2549	2394
	M1	0	1294	5220	0	651	2616	4	2302	8
	M2	2209	1176	4833	0	610	2436	0	2109	0
	EOT/M6	1788	967	3861	0	504	2028	1103	0	28
RePORT Indonesia	Baseline	1680	801	1411	0	451	1936	920	425	616
	M1	0	598	1002	0	338	1368	0	227	4
	M2	0	548	911	0	312	1261	0	173	4
	EOT/M6	0	474	719	0	243	984	486	118	0
RePORT Philippines (UPM)	Baseline	2220	1636	4372	4560	561	4331	2180	1187	1068
	M1	-	1340	3972	3952	497	3959	-	1115	261
	M2	-	1238	3624	3640	455	3607	-	1036	28
	EOT/M6	-	617	1804	1808	225	1760	864	307	8
Philippines (DLSMHSI) (MDR Cases)	Baseline	632	374	792	-	144	1192	624	580	260
	M1	-	322	696	-	112	984	-	487	-
	M1-M6	-	215	480	-	63	672	-	340	-
	EOT/M6	-	271	496	-	59	496	248	-	-
RePORT South Africa	Baseline	867	583	1720	1592	880	2892	1092	1641	852
	M1	222	362	613	1055	429	2020	120	594	48
	M2	488	359	1226	721	643	1930	60	428	12
	EOT/M6	28	279	216	545	145	852	548	319	24
TOTAL		19541	21186	80933	17873	13101	72325	9094	28651	11005

Table 6	Cohort B - Household Contacts	
	Date Enrollment Completed (yyyy-mm-dd)	Sample Size Enrolled (n)
RePORT Brazil	2015-06-01	1928
RePORT China	NA	0
RePORT India	2017-04-10	898
RePORT Indonesia	NA	0
RePORT Philippines - UPM-NIH	2022-11-22	686
RePORT Philippines - DLSMHSI	2022-03-03	163
RePORT South Africa	2017-08-03	637
TOTAL		4312

Table 7	Cohort B - Household Contacts - Enrollment Demographics					
	Total Enrolled (n)	Adult Males (n, %)*	Adult Females (n), %)*	Adults Median Age (yrs)	Children < 18 years of age (n)	IGRA+ (n)
RePORT Brazil	1928	784 (40.7%)	1144, (59.3%)	40	531	828
RePORT China	NA	NA	NA	NA	NA	NA
RePORT India	898	334 (37.2%)	498 (55.5%)	29	130	503
RePORT Indonesia	NA	NA	NA	NA	NA	NA
RePORT Philippines - UPM-NIH	686	288 (42.0%)	398 (58.0%)	39	326	193
RePORT Philippines = DLSMHSI	163	33 (35%)	62 (65%)	37	68	63
RePORT South Africa	637	247 (68%%)	116 (32%)	32	111	173
TOTAL	4312	1686 (43%)	2218 (57%)		1137	1760

*Some sites may have included children under 18 years of age.

Table 8	Cohort B - Household Contacts- Protocol Visits				
	Baseline (n)	Mos 3, 4, 6 (n)	Month 12 (n)	Month 24 (n)	TB Activation Evaluation (n)
RePORT Brazil	1928	1534	1470	1390	25
RePORT China	NA	NA	NA	NA	NA
RePORT India	898	723	720	556	18
RePORT Indonesia	NA	NA	NA	NA	NA
RePORT Philippines - UPM-NIH	686	2447	527	322	46
RePORT Philippines = DLSMHSI	163	156	144	121	8
RePORT South Africa	637	533	323	12	3
TOTAL	4312	5393	3184	2401	100

Table 9 Cohort B - Household Contacts - Outcomes

	RePORT Brazil (n)	RePORT China (n)	RePORT India (n)	RePORT Indonesia (n)	RePORT Philippines UPM (n)	RePORT Philippines DLSMHSI (n)	RePORT South Africa (n)	TOTAL (n)
No TB	1394	NA	688	NA	316	122	170	2690
Definite Case	13	NA	9	NA	2	2	41	67
Probable Case	4	NA	7	NA	4	6	0	21
Possible Case	8	NA	1	NA	41	0	1	51
Death	9	NA	4	NA	4	1	3	21
Lost to Follow-up	404	NA	155	NA	29	5	422	1015
Total	1832	0	864	0	396	136	637	3865

Table 10 Cohort B - Household Contacts Biorepository & Aliquots Per Site

		Whole Blood (EDTA) - DNA	Whole Blood (Heparin) - PBMC	Whole Blood (Heparin) - Plasma	Whole Blood (QFT 3rd Gen)	Whole Blood (QFT+, 4th gen)	Whole Blood - PAXgene RNA	Urine	Saliva	Sputum	MTB Isolate
RePORT Brazil	Baseline	7706	4075	19195	1798	5806	1765	18729	NA	NA	NA
	M1										
	M2					Not Applicable					
	EOT/M6	NA	3114	14935	700	3241	1362	14588	NA	NA	NA
RePORT China	Baseline										
	M1										
	M2					Not Applicable					
	EOT/M6										
RePORT India	Baseline	2302	2072	6896	898	0	2540	3569	2211	0	0
	M4-m6	446	289	986	138	0	379	556	298	0	0
	M12	542	389	1300	169	0	488	683	451	0	0
	M24	31	22	59	10	0	50	40	21	0	0
RePORT Indonesia	Baseline										
	M1										
	M2					Not Applicable					
	EOT/M6										
RePORT Philippines - UPM-NIH	Baseline	-	2117	4829	-	5112	636	4729	2261	-	-
	M1										
	M2					Not Applicable					
	EOT/M6										
RePORT Philippines - DLSMHSI	Baseline	656	356	736	-	1312	164	1176	633	-	-
	M1										
	M2					Not Applicable					
	EOT/M6										
RePORT South Africa	Baseline	114	1925	1976	3585	0	483	3662	2415	1364	70
	M4-M6	0	0	0	231	0	1	12	8	475	0
	M12	0	0	0	8	0	0	0	0	52	0
	M24	0	0	0	0	0	0	0	0	12	0
TOTAL		11797	14359	50912	7537	15471	7868	47744	8298	1903	70

RePORT International Network
Data Tables: Phase 2 (as of July 28th, 2023)

Table 1	Cohort A - TB Index Cases	
	Date of Enrollment Update (YYYY-MM-DD)	Sample Size Enrolled (n)
RePORT Brazil	2023-07-28	237
RePORT China		NA
RePORT India	2022-01-14	302
RePORT Indonesia		NA
RePORT Philippines		NA
Philippines - DLSMHI (MDR-TB)		NA
RePORT South Africa	2023-07-25	993
TOTAL		1532

Table 2	Cohort A - TB Index Cases - Enrollment Demographics					
	Total Enrolled (n)	Adult Males (n, %)*	Adult Females (n, %)*	Adults Median Age (yrs)	Children <18 years of age (n)	Participants with HIV (n)
RePORT Brazil	237	135 (57%)	89 (36%)	38	13	46
RePORT China	NA	NA	NA	NA	NA	NA
RePORT India	302	203 (67.2%)	99 (32.8%)	43	0	4
RePORT Indonesia	NA	NA	NA	NA	NA	NA
RePORT Philippines	NA	NA	NA	NA	NA	NA
Philippines - DLSMHI (MDR-TB)	NA	NA	NA	NA	NA	NA
RePORT South Africa	993	475 (47.8%)	393 (39.6%)	37.4	120	260
TOTAL	1532	817 (53.1%)	581 (37.9%)		133	310

*Some sites may not have gender information for a small number of participants

Table 3	Cohort A - TB Index Cases - Protocol Visits				
	Baseline (n)	Visit 1 (n)	Visit 2 (n)	End of Tx or (Month 6) (n)	Post TX Follow-up (12 months+) (n)
RePORT Brazil	237	203	181	92	20
RePORT China	NA	NA	NA	NA	NA
RePORT India*	302	237	186	100	3
RePORT Indonesia	NA	NA	NA	NA	NA
RePORT Philippines	NA	NA	NA	NA	NA
Philippines - DLSMHI (MDR-TB)	NA	NA	NA	NA	NA
RePORT South Africa	993	386	386	289	6MPOST - 138; 12MPOST - 98
TOTAL	1532	826	753	481	

*Post Treatment Follow-up (6 months post tx) n=46, Treatment Failures/Relapse n= 3

Table 4 Cohort A - TB Index Cases - Outcomes

	RePORT Brazil (n)	RePORT China (n)	RePORT India (n)	RePORT Indonesia (n)	RePORT Philippines (UPM) (n)	RePORT Philippines (DeLaSalle) MDR Cases (n)	RePORT South Africa (n)*	TOTAL (n)
Bacterioplogic Cure	19	NA	4	NA	NA	NA	20	43
Bacteriologic Status Indeterminate	3	NA	0	NA	NA	NA	1	4
Bacteriologic Failure	1	NA	1	NA	NA	NA		2
Bacteriologic Relapse	0	NA	3	NA	NA	NA		3
Not Tuberculosis	59	NA	0	NA	NA	NA	485	544
Death (if not bacteriologic/clinical outcomes)	3	NA	6	NA	NA	NA	6	15
Treatment Incomplete	20	NA	3	NA	NA	NA	2	25
Loss to Follow-up*		NA	7	NA	NA	NA	20	27
Not Evaluated	NA	NA		NA	NA	NA	411	411
Other	51	NA	28	NA	NA	NA	47	126
Moved out of Area	6	NA	5	NA	NA	NA	1	12
MTB Negative	22	NA	25	NA	NA	NA		47
Ineligible	0	NA	3	NA	NA	NA		3
Total	184		85				993	1262

*RePORT South Africa: Preliminary outcomes; all outcomes still need to be adjudicated per ongoing follow-ups and outstanding mycobacteriologic results

**RePORT Brazil: Lost to follow-up is combined with Treatment Incomplete

Table 5 Cohort A - TB Index Cases Biorepository & Aliquots Per Site

		Whole Blood (EDTA) - DNA	Whole Blood (Heparin) - PBMC*	Whole Blood (Heparin) - Plasma**	Whloe Blood (QFT+)	Whole Blood - PAXgene RNA	Urine	Saliva	Sputum	MTB Isolate
RePORT Brazil	Baseline	936	923	2360	NA	238	2340	NA	725	416
	M1	0	0	2010	NA	4	0	NA	423	104
	M2	12	688	1764	NA	177	1751	NA	333	8
	EOT/M6	4	347	918	NA	91	918	NA	210	0
RePORT China	Baseline									
	M1					Not Applicable				
	M2									
	EOT/M6									
RePORT India	Baseline	759	254	2156	NA	266	1048	659	859	736
	M1	NA	185	1589	NA	203	814	NA	629	92
	M2	NA	157	1113	NA	146	583	NA	445	16
	EOT/M6	262	96	660	NA	92	360	185	46	8
RePORT Indonesia	Baseline									
	M1					Not Applicable				
	M2									
	EOT/M6									
RePORT Philippines UPM	Baseline									
	M1					Not Applicable				
	M2									
	EOT/M6									
REPORT Philippines (DLSMHSI) (MDR Cases)	Baseline									
	M1					Not Applicable				
	M2*									
	EOT/M6									
RePORT South Africa	Baseline	2011	1193	777	NA	760	748	NA	1432	NA
	M1	4	364	197	NA	195	197	NA	315	NA
	M2	0	365	204	NA	204	202	NA	287	NA
	EOT/M6	5	345	159	NA	158	158	NA	222	NA
TOTAL		3993	4917	13907	0	2534	9119	844	5926	1379

*In RePORT South Africa, whole blood CPT vials + whole blood heparin tubes

**In RePORT South Africa, serum counts

Table 6	Cohort B - Household Contacts	
	Date of Enrollment Update (YYYY-MM-DD)	Sample Size Enrolled (n)
RePORT Brazil	2023-07-28	61
RePORT China	NA	NA
RePORT India	2021-12-30	295
RePORT Indonesia	NA	NA
RePORT Philippines - UPM-NIH	NA	NA
RePORT Philippines - DLSMHSI	NA	NA
RePORT South Africa	2023-07-25	991
TOTAL		1347

Table 7	Cohort B - Household Contacts - Enrollment Demographics					
	Total Enrolled (n)	Adult Males (n, %)*	Adult Females (n, %)*	Adults Median Age (yrs)	Children < 18 years of age (n)	IGRA+ (n)
RePORT Brazil	61	19 (31.1%)	29 (47.5%)	45.9	13	16
RePORT China	NA	NA	NA	NA	NA	NA
RePORT India	295	143 (48.5%)	152 (51.5%)	36	14	112
RePORT Indonesia	NA	NA	NA	NA	NA	NA
RePORT Philippines - UPM-NIH	NA	NA	NA	NA	NA	NA
RePORT Philippines = DLSMHSI	NA	NA	NA	NA	NA	NA
RePORT South Africa	991	339 (34.2%)	634 (64.0%)	34.8	18	NA
TOTAL	1347	501 (37.1%)	815 (60.5%)		45	128

*Some sites may have included children under 18 years of age.

Table 8	Cohort B - Household Contacts- Protocol Visits				
	Baseline (n)	Mos 3, 4, 6 (n)	Month 12 (n)	Month 24 (n)	TB Activation Evaluation (n)
RePORT Brazil	61	0	0	0	0
RePORT China	NA	NA	NA	NA	NA
RePORT India	295	129	13	0	2
RePORT Indonesia	NA	NA	NA	NA	NA
RePORT Philippines - UPM-NIH	NA	NA	NA	NA	NA
RePORT Philippines = DLSMHSI	NA	NA	NA	NA	NA
RePORT South Africa	991	743	726	NA	46
TOTAL	1347	872	739	0	48

Table 9 Cohort B - Household Contacts - Outcomes

	RePORT Brazil (n)	RePORT China (n)	RePORT India (n)	RePORT Indonesia (n)	RePORT Philippines UPM (n)	RePORT Philippines DeLaSalle (n)	RePORT South Africa* (n)	TOTAL (n)
No TB	0	NA		NA	NA	NA	702	702
Definite Case**	0	NA	1	NA	NA	NA	67	68
Probable Case	0	NA	1	NA	NA	NA	0	1
Possible Case	0	NA		NA	NA	NA	0	0
Death	0	NA		NA	NA	NA	6	6
Lost to Follow-up/Unknown	0	NA	11	NA	NA	NA	216	227
Total	0	0	13	0	0	0	991	1004

*RePORT South Africa: Preliminary outcomes

**RePORT South Africa: Baseline TB positive- 50; TB Activation= 17

Table 10 Cohort B - Household Contacts Biorepository & Aliquots Per Site

		Whole Blood (EDTA) - DNA	Whole Blood (Heparin) - PBMC*	Whole Blood (Heparin) - Plasma**	Whole Blood (QFT 3rd Gen)	Whole Blood (QFT+, 4th gen)	Whole Blood - PAXgene RNA	Urine	Saliva	Sputum	MTB Isolate
RePORT Brazil	Baseline	254	249	620	NA	992	62	620	NA	0	0
	M1	0	0	0	NA	0	0	0	NA	0	0
	M2	0	0	0	NA	0	0	0	NA	0	0
	EOT/M6	0	0	0	NA	0	0	0	NA	0	0
RePORT China	Baseline										
	M1					Not Applicable					
	M2										
	EOT/M6										
RePORT India	Baseline	295	154	1176		295	281	64	54	988	
	M4-m6		83	440		106	109	4			
	M12		14	44		12	11				
	M24										
RePORT Indonesia	Baseline										
	M1					Not Applicable					
	M2										
	EOT/M6										
RePORT Philippines - UPM-NIH	Baseline										
	M1					Not Applicable					
	M2										
	EOT/M6										
RePORT Philippines - DLSMHSI	Baseline										
	M1					Not Applicable					
	M2										
	EOT/M6										
RePORT South Africa	Baseline	1097	1594	1412	NA	3820	976	971	NA	1416	NA
	M4-M6										
	M12										
	M24										
TOTAL		1646	2094	3692	0	5225	1439	1659	54	2404	0

*In RePORT SA, whole blood CPT vials

**In RePORT SA, serum counts

TB-RICC DATA PRE-MEETING AGENDA

Venue: *LISBOA Ball Room, Radisson Blu Resort Goa*

Cavelossim, Beach, Mobor Beach, Goa 403731, India

TUESDAY, SEPTEMBER 5TH

9:00 am **Welcome / Goals of the meeting** [Stephany]

9:15 am **Brief Introductions** [all]

9:30 am **RePORT Phase I Update**

- Summary of harmonized Cohort A data [Stephany, Priyal, Sri Ram]
- Subjective variable mappings [Marina, Soyeon, Priyal]
- *Group discussion:* Addressing current challenges and capacity for data/specimen linkage and harmonization, use of Cohort B

10:30 am **Coffee/Tea/Juice Break**

10:45 am **RePORT International Project Updates and Data Discussion (15 minutes each)**

- Epidemiology and Adherence Protocol Update [Yuri, Nikhil, Valeria, Sri Ram]
- Biomarkers Protocol [Sheetal, Padmini, Bruno, Tom, Gerhard]

11:30 am **Technical Launch Kit for new RePORT sites**

- Components (REDCap, FreezerPro, training, SOPs) [Stephany]
- "Virtual Learning Room" [Alex]
- *Group discussion:* Recommendations for resources, training, and requirements, based on network experience

12:30 pm **Lunch**

1:45 pm **RePORT Phase II Data Planning**

- *Group discussion:* Goals for Phase II mapping and data harmonization, integration of Phase I and Phase II data, timelines for data requests
- Data workflow with Frontier Science support [Alex]

2:30 pm **Future Initiatives**

- Requesting data counts: conference booklets, quarterly enrollment update, and a minimum shared dataset for internal Data Dashboard [Soyeon, Stephany]
- Data QA/QC plans [Frontier/group discussion]
- Upcoming Common Protocol revisions and shared CRFs [Ann, Stephany]

3:15 pm **Coffee/Tea/Juice Break**

3:30 pm **Open discussion for data and technical topics [all]**

4:30 pm **Meeting adjourned**

7th Annual Regional Prospective Observational Research in Tuberculosis (RePORT) International Meeting

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